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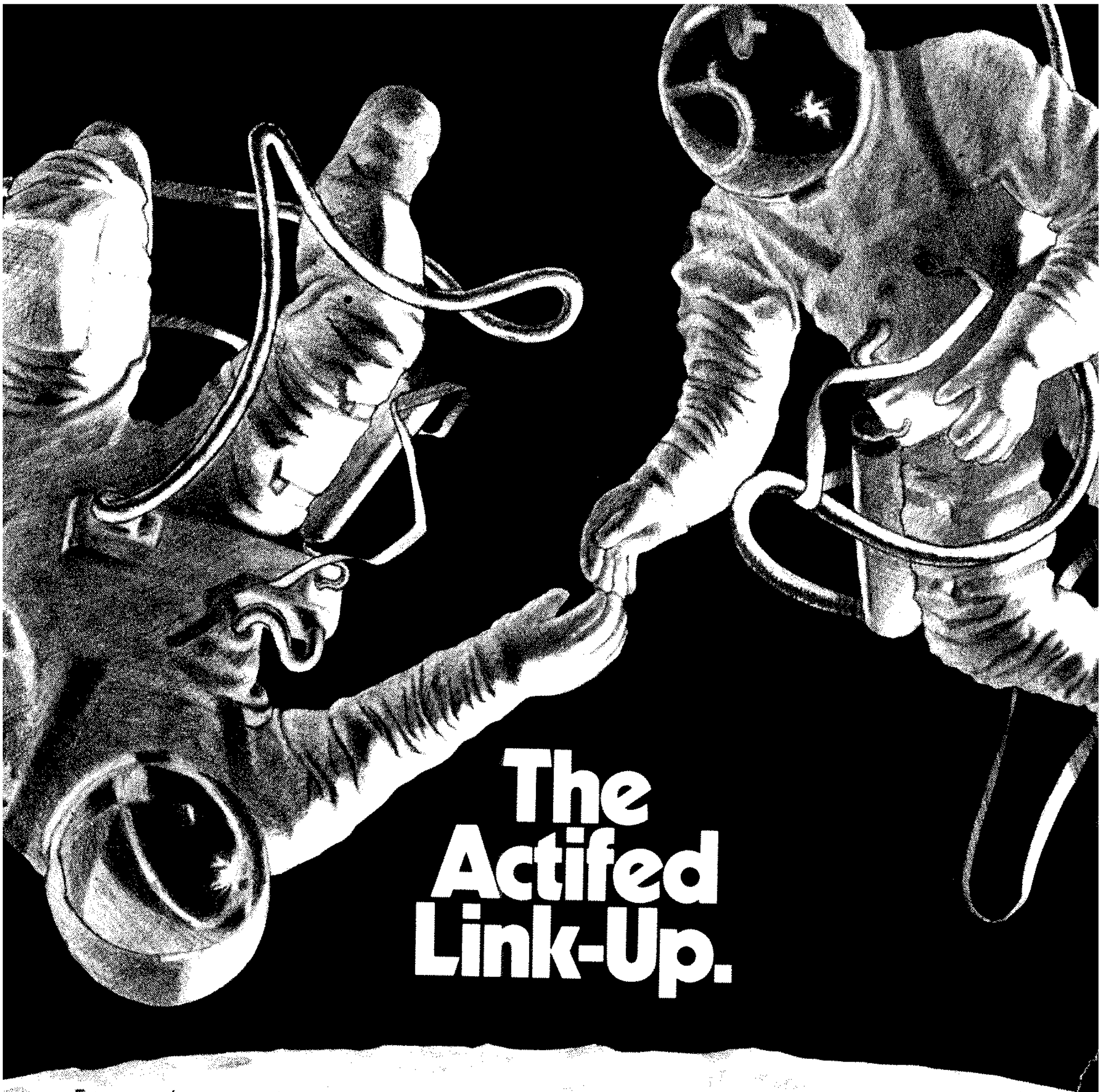

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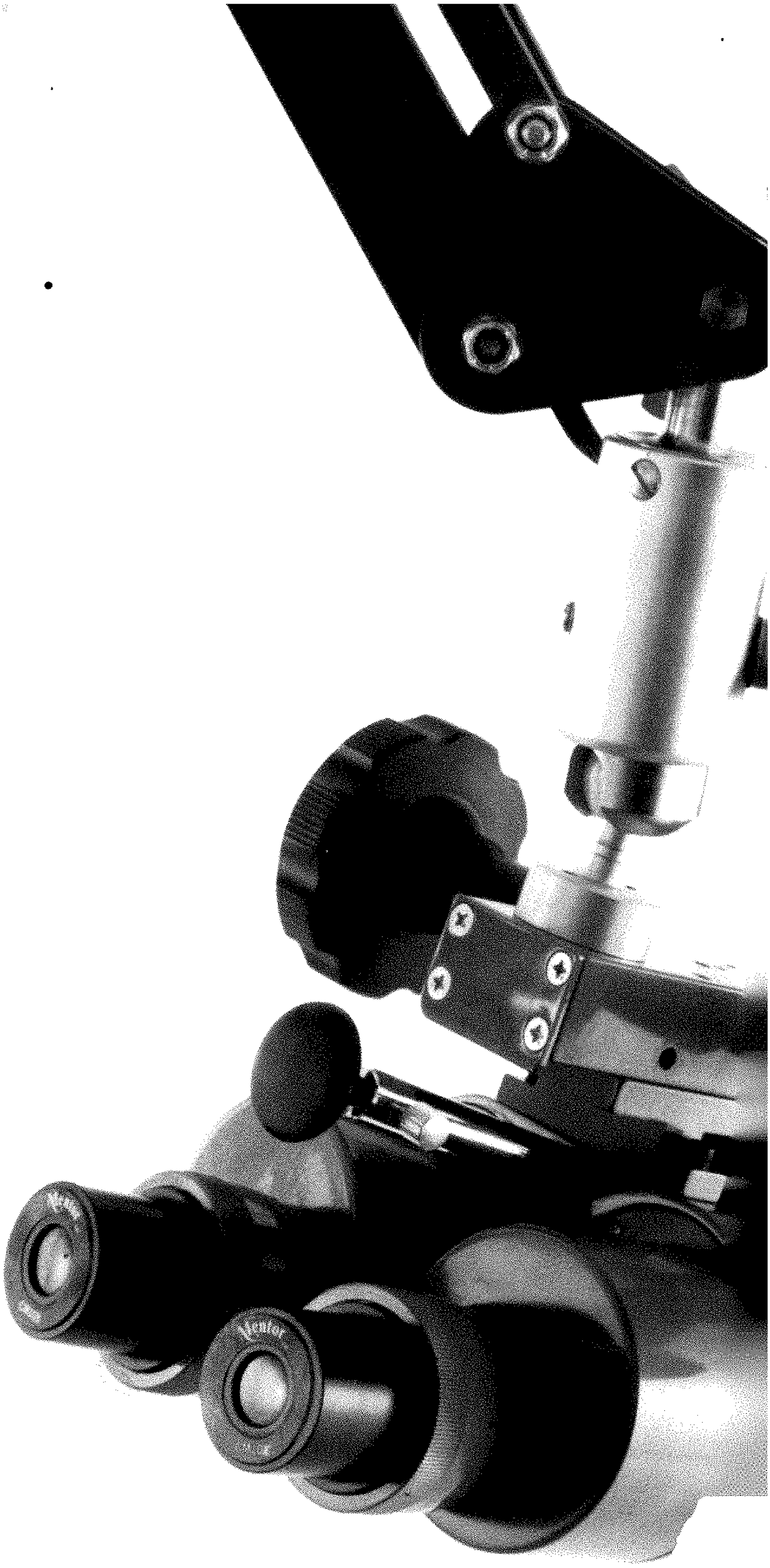
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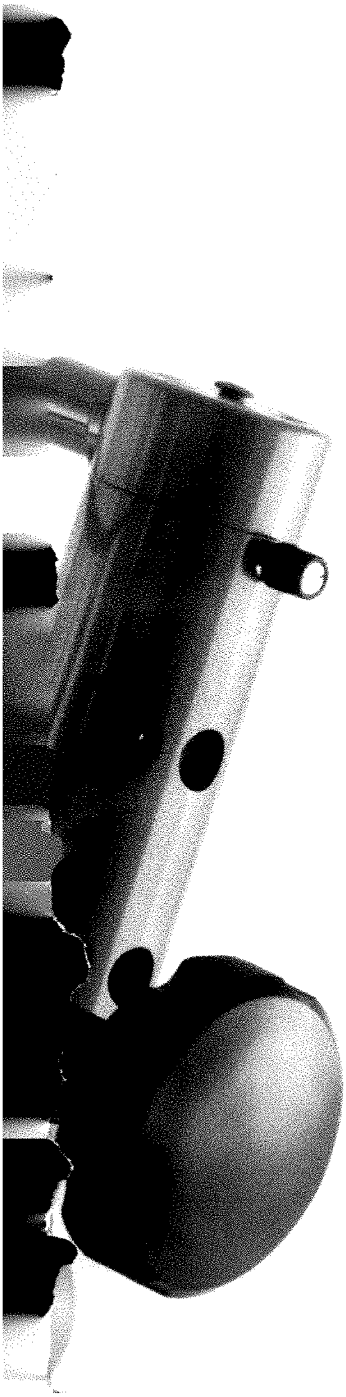

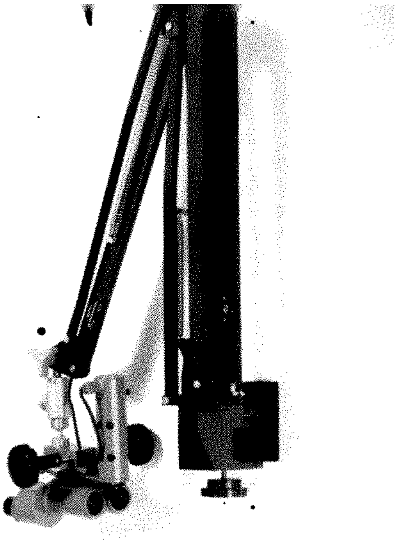

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Probably effective: For the symptomatic treatment of seasonal (hay fever) and perennial allergic rhinitis; vasomotor rhinitis; allergic conjunctivitis due to inhalant allergens and foods; mild, uncomplicated allergic skin manifestations of urticaria and angioedema; dermographism; as therapy for anaphylactic reactions adjunctive to epinephrine and other standard measures after the acute manifestations have been controlled.

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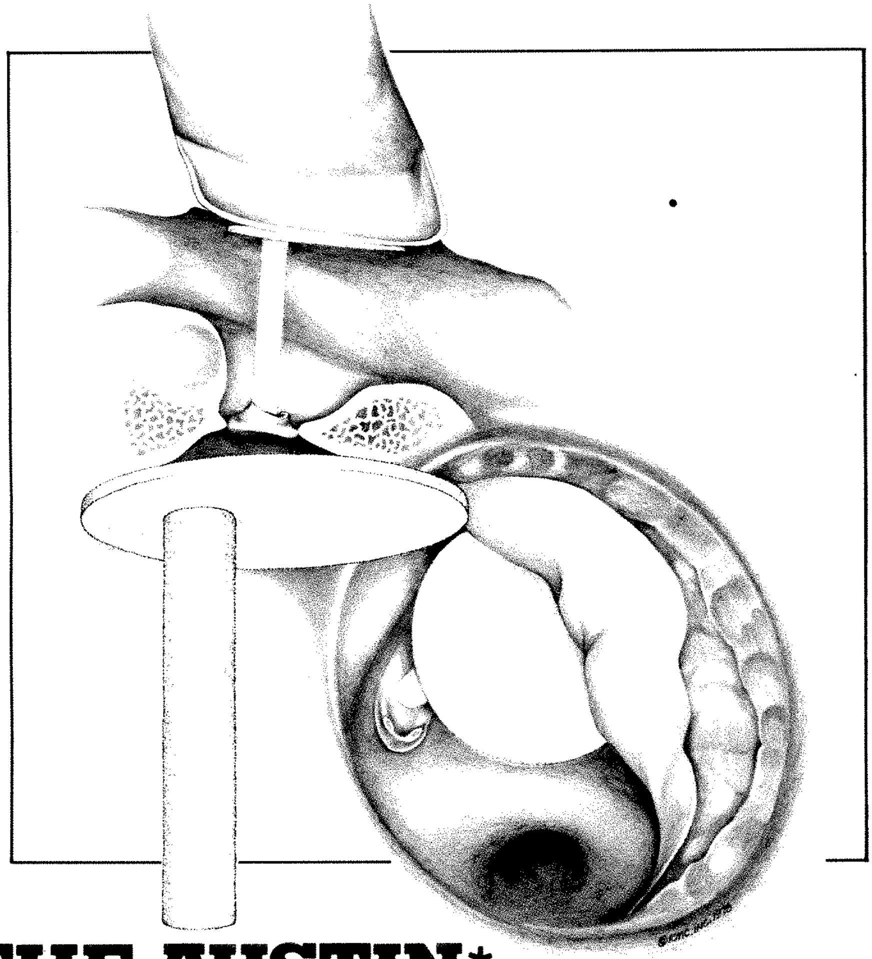

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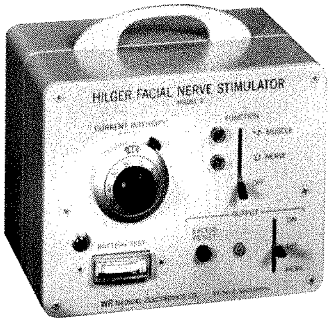

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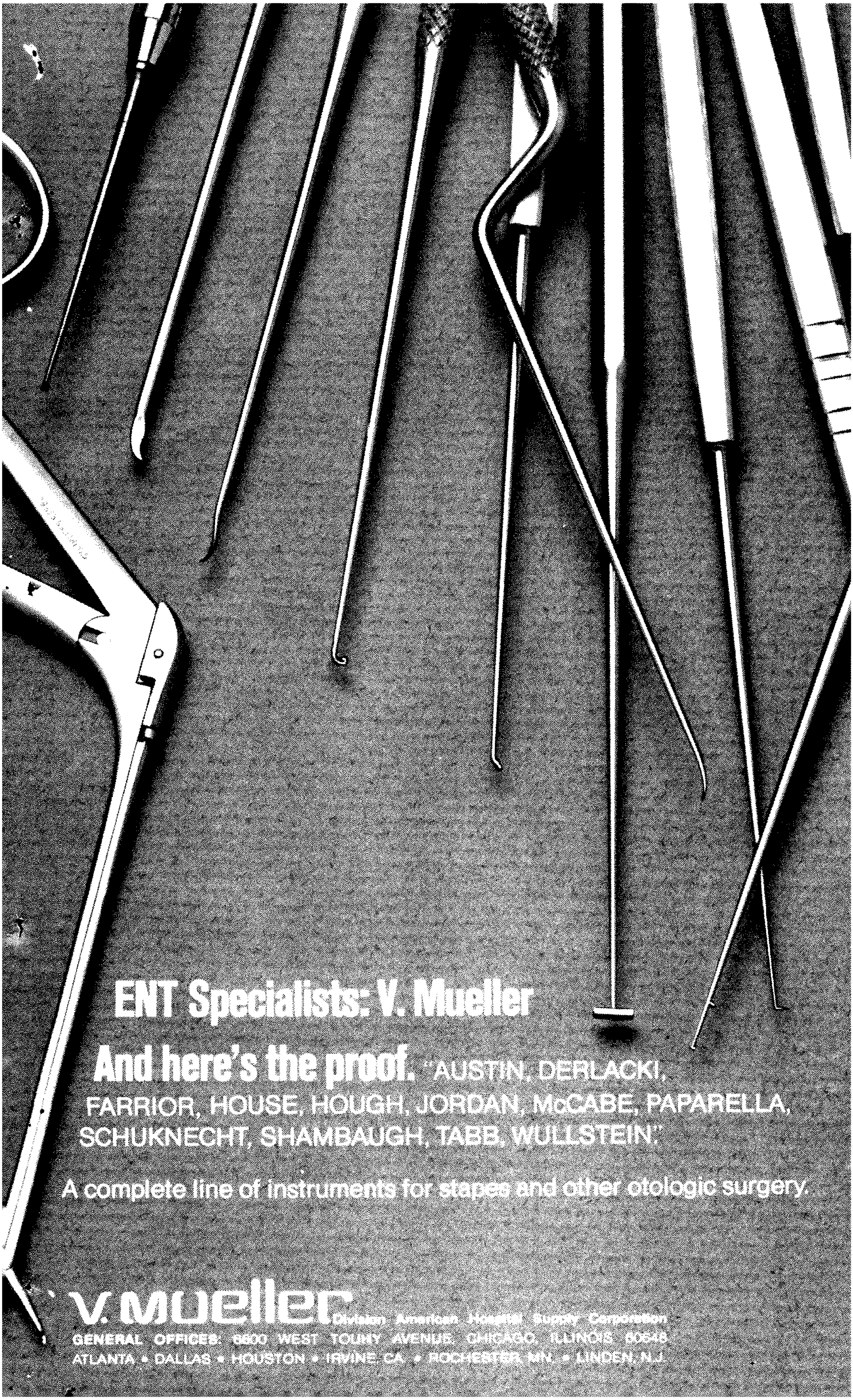

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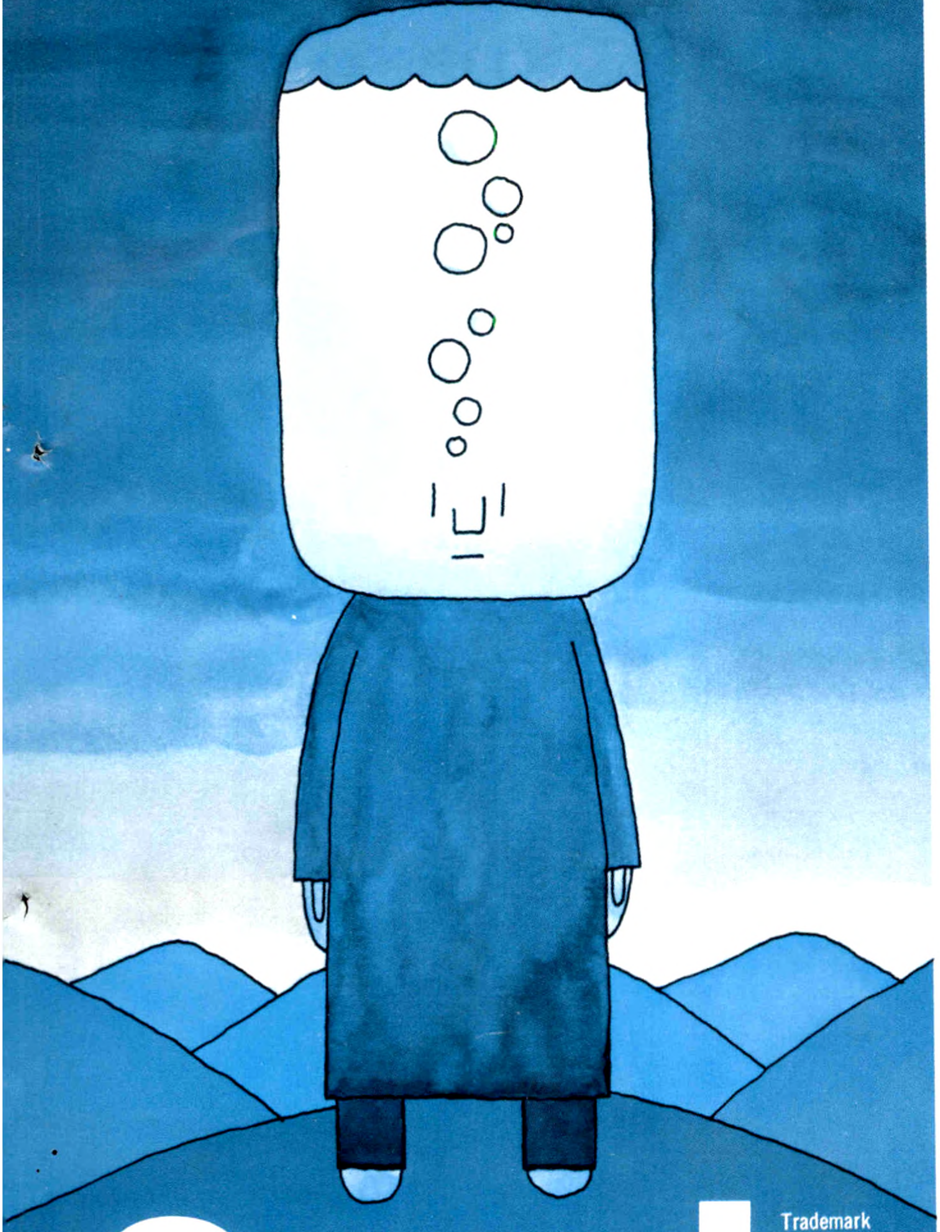

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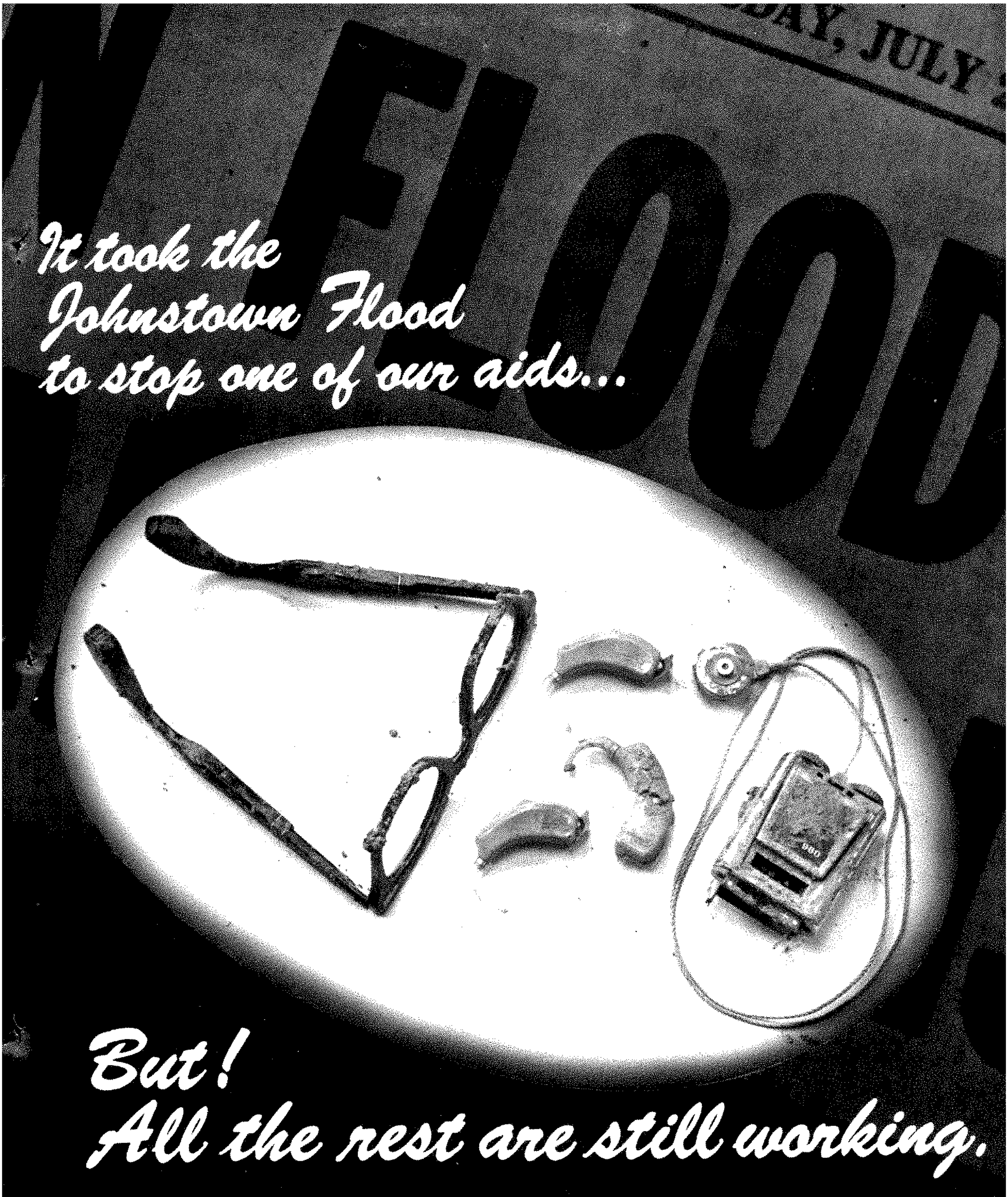

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EDITORIAL

We have just completed one of the happiest and most successful years both from an editorial and a scientific standpoint, and must take a moment from our busy lives to give thanks to all the medical, editorial, administrative and production personnel for their important contributions.

The past year has been one of considerable introspection, retrospection, and research into how the *ANNALS* can better carry out its mission of keeping practitioners and scientists of otolaryngology and its allied fields the best informed readers in the world. Reader polls and close consultation with the members of our boards have been carried out. One result of this activity is the development and expansion of clinical reports and reviews in areas of interest particularly to our young practitioners and residents. As this emerges, we welcome the response and advice of our readers in this and any other area of mutual interest. We shall continue to search for means of making the *ANNALS* interesting to practitioners, investigators and students while attempting to maintain a balance between clinical and research papers. Fortunately, the *ANNALS* continues to be supplied with an abundance of good papers from all over the world and their authors receive an impressive number of requests for reprints.

After many years of consideration we have finally instituted a plan for rotating Editorial and Review Boards for the *ANNALS*. This will be introduced slowly over a period of months with the objective of establishing smaller but more active Boards. It has been of much concern to us in the past that we have received the help and cooperation of a large number of individuals, but because of our previous appointment tenures we have been able to give proper recognition to only a few. We hope that we can correct this in the future.

One of the most perplexing problems confronting all publishers is the new copyright law which took effect on January 1, 1978. It is a complex unsatisfactory compromise of a large number of problems which have plagued publishers, librarians, teachers and many others. The *ANNALS* is interested in disseminating scientific information and is not desirous of restricting the use of its published material. It is obvious, however, that we cannot function without some protection against those who would misuse or make profit from the material which we edit, print and distribute at great expense. We therefore ask our essayists to bear with us as we attempt to resolve these problems.

Our plan for providing the Supplements as a vehicle for distributing excessively long and complicated papers without cost to our subscribers has continued to bring us many kudos and much pleasure. Essayists from all over the world who have submitted Supplements have provided us challenges and problems, most of which we have been able to resolve. We anticipate another excellent series of Supplements in 1978.

There seems to be evidence in our country today of a restatement of those moral and ethical standards which made this country the great leader that it is. With the ongoing negotiations in the Middle East as we go to press, perhaps we are on the threshold of a new era of peace which will allow the countries of the world to cooperate in bringing about a better world for all of us. Let us pray and hope for enlightenment, understanding and love for all people as we attempt to cope with our problems in 1978.

Ben H. Senturia, MD
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Ann Otol 87:1978

CRITICAL LOOK AT THE CLASSIFICATION OF MAXILLARY SINUS CARCINOMATA

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SUMMARY — All the classification systems at present adopted for use in carcinoma of the maxillary sinus suffer from both intrinsic inaccuracies and an apparent failure to relate T (extent of primary tumor) categories to clinical experience of the spread of these tumors. Three systems are critically analyzed in relation to personal experience of 86 patients with sinus carcinoma and a fourth system proposed as a compromise solution to this problem.

The practice of dividing cancer cases into groups according to so-called "stages" arose from the fact that crude survival, or apparent recovery rates were higher for cases in which the disease was localized than for those in which the disease had extended beyond the organ of origin.[1] Unfortunately, the clinical oncologist is well aware that the extent of any tumor at diagnosis is a reflection of rate of growth, histological type, tumor-host relationship and the difficulty of clinical diagnosis. Consequently, there must always be inherent weaknesses in any system of classification and these will vary with each anatomical site. It is important that each deficiency is appreciated and, where possible, evaluated, for it is possible that in certain specific instances they may render a particular classification virtually useless, if not actually misleading.

The purposes of classification are many but primarily serve to facilitate exchange of information between treatment centers and to aid oncologists in planning therapy. Even if it were possible for each clinician to objectively assess any specific tumor with complete accuracy, there would remain the permanent difficulties of inaccessibility—the breast being more satisfactory than stomach or kidney, for example. Sites such as the paranasal sinuses can only be visualized radiologically unless the tumor has extended outside surrounding bony walls. Consequently, diagnosis is usually late and accurate delineation of tumor extent difficult. Despite this, there is a common value in the usage of all systems of classification—increased accuracy of record keeping. Such information forms the basis of all classifications, both present and in the future, and enables retrospective analysis and comparisons to be performed with reasonable accuracy.

Malignant tumors arising within the paranasal sinuses are uncommon but no less important and challenging than many other tumors found in the head and neck. Most sites in this region have now been classified but confusion and disagreement remain regarding the maxillary sinus, the most common site of malignancy within the paranasal sinuses. The reasons for this are many and include lack of personal experience and the inherent difficulties of accurate evaluation, particularly as most patients present with late stage disease. It has long been appreciated that tumors situated in the posterior-superior part of the maxillary sinus, defined by Ohngren of Stockholm[2] as being above an imaginary plane extending from the medial canthus to the angle of the mandible, carry a worse prognosis than those situated anteroinferiorly. The reason for this, ignoring variations in histopathology, are quite clear being primarily related to the difficulties of resecting disease from the important structures related to this part of the maxillary sinus, such as or-

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bit, cribriform plate, and pterygoid region. Tumors also present later in this situation and will therefore be more extensive on diagnosis. Ohngren's observations were basically correct, but his classification, which included variations in histology, was over-complicated and valueless in clinical practice.

Lederman[3] has modified the system proposed by Sebileau[4] in 1906, dividing the upper jaw into supra-, meso- and infrastructure by means of parallel lines through floor of orbit and the floor of the maxillary sinus. These two lines are supplemented by vertical lines extending down from the medial orbital walls on each side to the floor of the nose. This has the merit of including both ethmoidal sinuses and tumors arising within the nasal passages and is therefore comprehensive and is based on considerable personal experience of sinus neoplasms. The American Joint Committee has, however, adopted a system which utilizes Ohngren's line, calling the region above the suprastructure and that below, infrastructure. Since Lederman's infrastructure is not really maxillary sinus at all, or at least very little of it, the confusion between these two systems could be considerable.

In Japan, Sakai *et al*,[5] have evolved a completely separate system of classification which appears to have successfully combined the disadvantages and inaccuracies of both preceding systems and their application of it to 709 patients with carcinoma of the maxillary sinus[6] emphasizes the inherent weakness and dangers of over imaginative and optimistic planning without consideration of the natural history of a particular tumor.

It is, of course, always easy, though not necessarily productive, to criticize the opinions of others but those experienced in the management of sinus neoplasms are well-aware of the difficulties and deficiencies of all three systems. There would appear to be some merit, therefore, in examining them all critically, but constructively, in the hope that from such an exercise would emerge a system which would be both clinically practical and reasonably accurate. Such an analysis is best carried out in the light of personal experience of managing a reasonable number of patients over a relatively short period of time, for retrospective analysis of large groups of patients suffers from the insurmountable weakness of variations in treatment policy, clinical and radiological assessment and often a failure to re-evaluate histopathological material or radiological films.

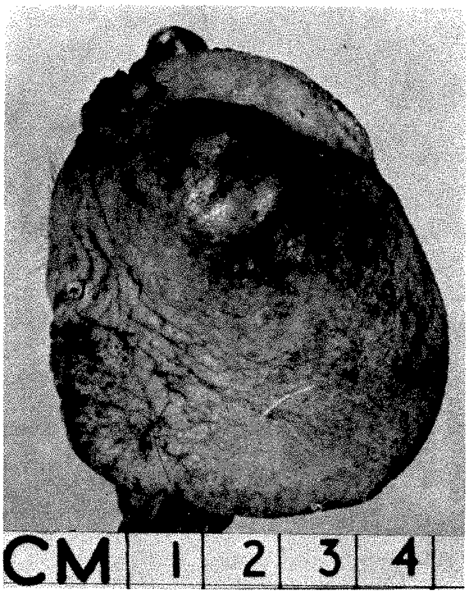

Fig. 1. Skin excised with tumor extension from maxillary antral carcinoma.

During 1960-1973 I personally cared for 132 patients with malignant disease arising in the maxillary and ethmoidal sinuses. It is not always possible to be certain of the site of origin of antro-ethmoidal neoplasms and the natural history of both adenocarcinoma and adenoid cystic carcinoma is such that, for the purpose of this particular exercise, and most TNM classifications, only the 86 patients with squamous carcinoma thought to arise primarily within the maxillary sinus will be considered.

This is not an attempt at presenting the results of treatment, variations in presenting symptoms, or other matters related to the natural history of this disease;[7] but rather to utilize my personal experience of the group to consider the relative values of several systems of classification.

Each patient in my own series was evaluated both clinically and radiologically, utilizing the most sophisticated techniques now available, including axial submento-vertical tomography—the only method of accurately determining involvement of the posterior ethmoidal cells and the margins of the optic foramen. All this information was meticulously recorded and both radiological films and histopathological material reevaluated. Except for the two patients with small tumors arising from the sinus floor which were treated by primary partial maxillectomy, all had curative doses of supravoltage radiotherapy, followed several weeks later by radical surgery. In every patient residual tumor was present and in the majority of patients it was possible to determine the original extent of the tumor, utilizing evidence of underlying bone destruction. Mucosal disease can never be determined accurately at any stage of treatment because of the existence of submucosal extension.

Failure to cure maxillary sinus cancer is primarily failure to eradicate extension of tumor outside the bony walls of the sinus. Only a few patients present with regional lymph node metastasis, 3.5% in this series, and even less develop systemic metastasis unless the patient is terminal. It is extension of tumor to the apex of the orbit, cribriform plate, and posterior ethmoid cells, pterygoid region or nasopharynx, which results in disease left *in situ*. Consequently, it is such extensions which must be determined prior to treatment and classified accordingly. Bony erosion within the limits of potential excision, such as the orbital floor, are obviously less serious if treated radically, and even involvement of facial skin may be successfully excised if care is taken to ensure adequate margins of resection (Figs. 1, 2). Removal of the cribriform plate area as described by Ketcham[8] can be effective providing involvement is minimal and the procedure is combined with the original oncological operation. If left too late, extension posteriorly to the optic chiasma will limit margins of resection, and therefore such involvement must still be considered a late stage in tumor development. Modern radiological techniques combined with thorough clinical examination will reveal gross areas of bone loss or invasion of contiguous structures. Less obvious involvement will remain undetected until revealed at subsequent surgery and thereby leads to errors in classification. One must conclude that attempts at classifying this tumor finitely are both impractical and unrealistic. We must therefore examine the three classifications presently in use with these restrictions in mind, and be prepared to discard any category that does not adequately fulfill a criteria of practicability. It should then be possible to assemble from the combined debris a useful and effective classification for international usage.

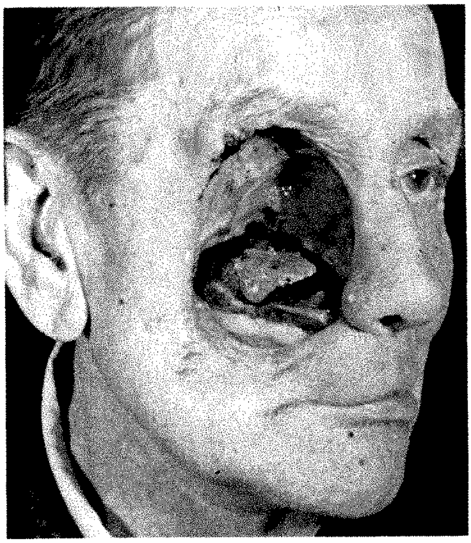

Fig. 2. Residual defect from excision of skin.

American Joint Committee 1976. Definition of "T" Category of the Maxillary Antrum.

T1. Tumor confined to the antral mucosa of the infrastructure with no bone erosion or destruction.

T2. Tumor confined to the suprastructure mucosa without bone destruction or to the infrastructure with destruction of medial or inferior bony walls only.

T3. More extensive tumor invading skin of cheek, orbit, anterior ethmoid sinuses, or pterygoid muscle.

T4. Massive tumor with invasion of cribriform plate, posterior ethmoids, sphenoid, nasopharynx, pterygoid plates, or base of skull.

Ohngren's line, a theoretical plane joining the medial canthus of the eye to the angle of the mandible, may be used to divide the maxillary antrum into an anterior-inferior portion, the infrastructure, and a superior-posterior portion, the suprastructure.

There is no fundamental objection to using an imaginary plan to divide the maxillary sinus into two parts if this serves a useful purpose. Since mucosal disease is not confined by such boundaries and it must be near impossible to be sure, even on direct inspection, that any particular neoplasm is restricted in the manner described as T1, this definition appears impracticable—even nonsensical (if bone is eroded it must also be destroyed!). A neoplasm confined to the mucosa alone without evidence of extra mucosal spread would be a more realistic T1, and these are, unfortunately, rare tumors, usually found accidentally.

T2 would now be replaced by "bone erosion of the infrastructure alone providing that this did not extend to the tuberosity to avoid jeopardizing the area of the pterygoid plates." T3 assumes some success with radical surgery and this certainly applies to facial skin, orbit if the apex is clear, and anterior ethmoids if this can ever be diagnosed with certainty. Involvement of the pterygopalatine fossa, and pterygoid muscle invasion is, in my experience, as serious as extension to the roof of the nose or nasopharynx. If not cured by radiotherapy it is rarely successfully removed surgically. Perhaps this whole region should be included within T4, indicating late incurable disease.

Lederman 1970. By the use of parallel horizontal and vertical lines, Lederman[3] has divided the whole upper jaw into supra- meso- and infrastructure. The maxillary antrum lies with the middle region (mesostructure) and three degrees of T for the primary squamous carcinoma can be recognized.

T1. Tumor limited to one sinus or a tissue of origin, *e.g.*, turbinate, septum, or nasal vestibule.

T2. Spread limited horizontally to the same region or two adjacent but vertically related regions.

T3. (a) Tumor involving three regions (with or without involvement of orbit). (b) Tumor extending beyond upper jaw, *e.g.*, nasopharynx, cranial cavity, pterygopalatine fossa, skin, or buccal cavity.

Early mucosal lesions confined to the sinus properly belong to T1 but T2 can cause confusion, in that, extension to the orbit or ethmoid would be classified along with the less serious inferior involvement of sinus floor or hard palate. Similarly, either would be equated with horizontal extension to the nose below the level of the middle turbinal. Such comparisons are not compatible with clinical experience and serve only to confuse.

T3a is an uncommon clinical situation and could well be excluded, leaving T3 to cover all advanced cases, although the prognostic significance of facial skin involvement alone is far less than invasion of nasopharynx or pterygopalatine fossa. However, this classification based on personal experience of approximately 350 patients has the merit of simplicity and coverage of the whole upper jaw.

Sakai 1974. The largest series of patients yet reported has been by Sakai *et al*[5] in 1976 (560 cases of maxillary sinus cancer). Unfortunately, the value of this experience has been largely negated by their adoption of yet another system of classification first proposed by Sakai and Hamasaki in 1967.[9]

No boundaries, planes, or subdivisions are employed, the maxillary sinus being defined as a simple anatomical entity. Extension of primary tumor is separated into the usual four divisions.

T1. Tumor confined to the maxillary sinus, with no evidence of bony involvement.

T2. Tumor causing destruction of the

bony wall, with the external periosteum remaining intact as a capsule and the surrounding tissue not invaded but only compressed. Minimal infiltration into the ethmoid cells and the exophytic tumor in the middle nasal meatus is included in this category.

T3. Tumor infiltrating deeply into the surrounding tissue by penetration of the external periosteum.

T4. Tumor extending to the base of skull, the nasopharynx and the maxilla of the opposite side.

An additional confusion and potential error is added by the use of a separate table describing the clinical features of each T grade depending upon the direction of tumor extension, *e.g.*, T2 supero-medial-mass in midnasal meatus, slight exopthalmos, minimal defect of orbital wall. If extension is inferolateral —T2 is bulging of upper gum, defect of inferolateral wall, *etc.*

Clinical or radiological detection of bone destruction with an intact periosteum and compression without invasion for all margins of the maxillary sinus is quite impossible with any degree of accuracy. Talk of "minimal" infiltration of the ethmoidal labyrinth can inspire no feeling of confidence in classification or classifiers suggesting a complete unawareness of the intrinsic problems of the spread of maxillary sinus cancer. T3 with deep infiltration of surrounding tissues suggests no separation of tumor extension superiorly or posteriorly when prognosis is far worse. Such lack of clarity can, of course, explain variations in published cure rates by including a disproportionate number of early cases along with later staged disease.

Reference once again to the author's attempts at correlating T grades with direction of tumor extension reveals such imprecise descriptions as "fairly intact pterygoid process, minimal defects of bony wall and swelling of the cheek without adhesion."

DISCUSSION

The underlying purpose of classifying malignant tumors must surely be to obtain homogenous, statistically equivalent groups of patients for the purpose of assessing, evaluating and comparing various therapeutic methods.[10] By definition the TNM system of classification is a clinical classification and as such is entirely dependent upon the clinical expertise and integrity of the responsible clinician. Ignoring the problems relating to the determination of involved regional lymph nodes or systemic metastasis, the essential problem to be faced in the classification of maxillary sinus cancer is, Can the clinician evaluate objectively the available information with sufficient accuracy to describe the dimensions and extent of the primary tumor? Are these criteria sufficient to formulate an indication of prognosis and, is the data recorded sufficiently accurately to enable retrospective analysis?

The limitations in clinical assessment of maxillary sinus cancer have already been emphasized and consequently, there can be little justification for erecting a complex system of classification based upon such unstable foundations. However, clinical experience has emphasized the importance of certain directions of tumor extension in relation to subsequent prognosis and it would therefore seem to be logical to base any system of classification upon such premises. Minor errors in assessment will continue to exist, as will variations in immune response and histopathology. Despite this, the oncologist would be left with a classification which was both practical, accurate, and closely related to the principal factors influencing prognosis.

With these considerations in mind and detailed analysis of the extent and routes of spread of tumor in the 86 patients personally treated by me, I suggest that the following T grouping might well be of more practical use than the three existing systems discussed previously.

T1. Tumor limited to the antral mucosa with no evidence of bone erosion.

T2. Bony erosion without evidence of involvement of facial skin, orbit, pterygopalatine fossa or ethmoidal labyrinth.

T3. Involvement of orbit, ethmoidal labyrinth or facial skin.

T4. Tumor extension to nasopharynx, sphenoidal sinus, cribriform plate or pterygopalatine fossa.

Utilizing the UICC proposals for N and M and thus grouping this series accordingly resulted in over 90% of the patients falling into Stage III or IV.

If one is to justify the proposals of yet another system of classification then it must satisfy the same critical examination that failed those at present in existence. T1 is adequate for those cases where the disease is confined to the sinus mucosa and where diagnosis is either accidental or because of an early significant symptom, such as unilateral epiphora or infraorbital neuralgia. There were three patients in my series fortunate enough to be in this category and all remain well at least five years post diagnosis.

In T2, providing surrounding structures are not grossly involved, bone erosion itself may not be unduly significant. Unfortunately, diagnosis is not usually possible until involvement has occurred but obviously there must be a stage prior to this where diagnosis is theoretically possible. It also includes inferior extension to involve the alveolus and hard palate. Providing the neoplasm has not extended to the maxillary tuberosity to jeopardize the pterygoid plates, then surgical excision is both practical and rewarding. Four patients were within this group and all remain alive. The following two groups include the majority of patients with maxillary sinus cancer and the overall poor long-term cure rates indicate the seriousness of both T3 and T4 lesions. Yet, an attempt at separation is of value since new methods of management, particularly combinations of chemotherapy with radiotherapy or surgery, may possibly be more effective in certain specific extensions of the primary tumor.

T3 involvement of the orbit, as such, should be adequately treated surgically, but apart from the intrinsic difficulties inherent in early detection, extension to the apex of the orbit presents an almost impossible technical problem. In addition, it is common for tumors within this group to have extended in other directions, such as the ethmoid or pterygopalatine fossa. If tumor is left *in situ* after preliminary curative dosage of radiotherapy, as is commonly the case, it is usually at the periphery of such extensions and may not be excisable. Involvement of the facial skin alone has not proved to be such a significant problem in my experience, though requiring a carefully controlled wide excision and a staged reconstruction.

In T4, unless there is massive tumor extension, differentiation between T3 and T4 tumors is not always possible. Involvement of the ethmoidal labyrinth must always carry the risk of extension to the closely adjoining cribriform plate, although cerebrospinal rhinorrhea has not occurred in any of my own patients. Excision of the pterygoid plates, preoperative trismus, or macroscopical tumor within the pterygopalatine fossa is, in my experience, virtually impossible to eradicate, though good palliation is possible following carefully planned and executed radical surgery. Along with extension from the posterior ethmoids to the nasopharynx, this disease falls naturally into the most extensive and serious group. Unlike other sites within the head and neck, it is not only the macroscopical size of the tumor which influences prognosis or indeed the likelihood of lymph node metastasis. A maxillary sinus full of tumor but without bone erosion is not as serious as a small extension into the ethmoidal labyrinth or pterygopalatine fossa. It is suggested therefore, than an informed consideration of those factors which influence the natural history of the spread of maxillary sinus cancer is a sounder foundation on which to build a system of classification than a fertile imagination or the accumulation of a vast collection of unreliable statistics. Such a system is proposed with the sole excuse that it is based upon a critical evaluation of a very personal series of patients whose treatment, I may add, has by no means been universally successful.

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EAR ANOMALIES ASSOCIATED WITH RENAL DYSPLASIA AND IMMUNODEFICIENCY DISEASE

A HISTOPATHOLOGICAL STUDY

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SUMMARY — The histopathologic study of the temporal bones of a case with low-set rudimentary auricles, without preauricular pits or cervical fistula is presented. Abnormalities of the middle and inner ear, fusion of the kidneys, hydrocephalus, short-limbed dwarfism and immunodeficiency are described. An abnormally low position of the middle cranial fossa in relation to the petrous pyramid was observed. The cochlea was of normal length. The modiolus was poorly developed with apparently normal population of ganglion cells and moderate diffuse hydrops of the cochlear duct and saccule. The stria vascularis was partially degenerated in the upper apical coil. Vestibular abnormalities included bilateral absence of common crus of the vertical canals and unusually high origin of endolymphatic aqueduct with no medial dilation present, the convoluted portion of the sac located beneath the dura.

The histopathology of the middle and inner ears in a female child with the autosomal dominant syndrome of preauricular pits, cervical fistulae and hearing loss, has been recently described.[1] Reports of at least 16 other families with this dominantly inherited syndrome have been listed[2-17] and an associated high incidence of renal anomalies has been noted. Gross anomalies of the external ear have been reported as part of several cases involving varying syndromes, each with an overlapping group of accompanying malformations.[18] The associated inner ear histopathology of these cases has been described in a limited number of instances.[19-24]

Recently, in our laboratory, a case with low-set rudimentary auricles without preauricular pits or neck fistulae was observed. Maldevelopment of the kidneys, hydrocephalus and short-limbed dwarfism were present.

The histopathological examination of the ears showed middle and inner ear pathology of comparative significance to that described in the previous case.[1]

CASE REPORT

A female child was born at full term to a 21-year-old mother and 23-year-old father. Pregnancy was normal. No undue nausea was observed. No medications were used except vitamins and aspirin. Birth weight was 1.6 kg. Multiple anomalies were noted at birth. These included low-set rudimentary auricles with almost no lobules, a prominent, beaked, pointed nose and prominent forehead. The head appeared large compared to the body and fontanelles were widely open. The face appeared relatively small, the mouth also small, and palate high with no cleft. The neck showed increased skin folds and was short. The chest, abdomen and genitalia appeared normal. The arms appeared relatively long. Bilateral simian creases were noted. Feet showed partial bilateral syndactyly of second and third toes. Due to the presence of such multiple anomalies, a chromosomal evaluation was performed but three different blood samples failed to show enough cell division of lymphocytes for analysis. Study of the patient's immune response

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From the section of Otolaryngology, Pritzker School of Medicine, University of Chicago, Chicago, Illinois. This study was supported in part by Grant 2-P01-NS-03358 from the National Institute of Neurological Diseases and Stroke and by the Research Fund of the American Otological Society, Inc.

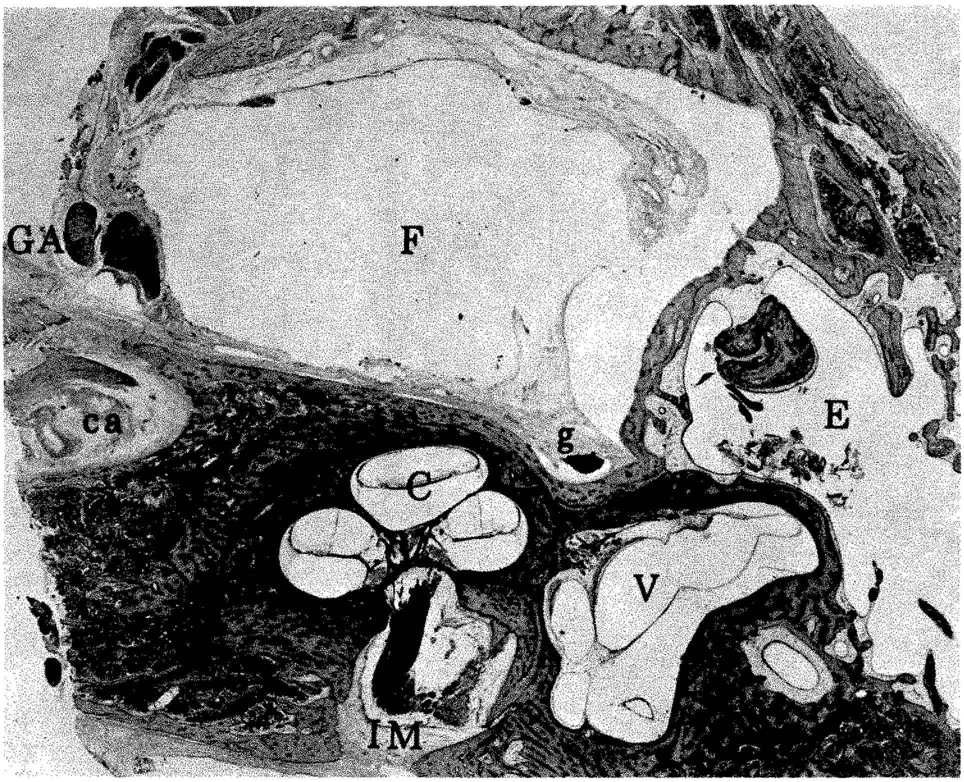

Fig. 1. Low power photomicrograph of the right temporal bone showing the low position of the middle cranial fossa (F), in relation to the epitympanum (E) and the cochlea (C). IM - Internal auditory meatus; V - Vestibule; ca - Carotid artery; g - Geniculate ganglion; GA - Gasserian ganglion. (H & E stain, X6.5)

was recommended. An air ventriculogram showed a dilated ventricular system. No air reached the fourth ventricle. The intravenous pyelogram showed the right kidney fused to the left kidney (crossed fused ectopy). A bone survey showed bilateral congenital dislocation of the hips and dysplastic acetabulae. Also, retarded ossification was noted particularly at the knees and feet. The lymphocytic responses to PHA stimulation was interpreted as low normal but was without delayed cutaneous hypersensitivity. The family history indicated that the child's father, paternal grandfather and certain other members of the family had short stature with narrow, beaked, and pointed noses The child's mother had dislocated hips at birth.

Death followed several days after a cardiac arrest during preparation for a shunt procedure. The autopsy examination demonstrated the following: severe hydrocephalus and agenesis of the corpus callosum, very few lymphocytes in the splenic white pulp and lymph nodes, acute lymphadenitis, fusion of kidneys to form a single kidney on the left, and renal abscesses, acute pyelonephritis, abnormal pulmonary lobulation and thymic lymphaplasia.

HISTOPATHOLOGY OF TEMPORAL BONES

Both temporal bones were removed 22 hours after death, fixed in 20% formaldehyde solution, decalcified with 1% nitric acid and embedded in celloidin. Serial 20μ thick sections were made and tracer sets of every fifth section were stained with H. and E.

RIGHT EAR

Low power view of sections through the upper part of the pyramid shows a middle cranial fossa abnormally located

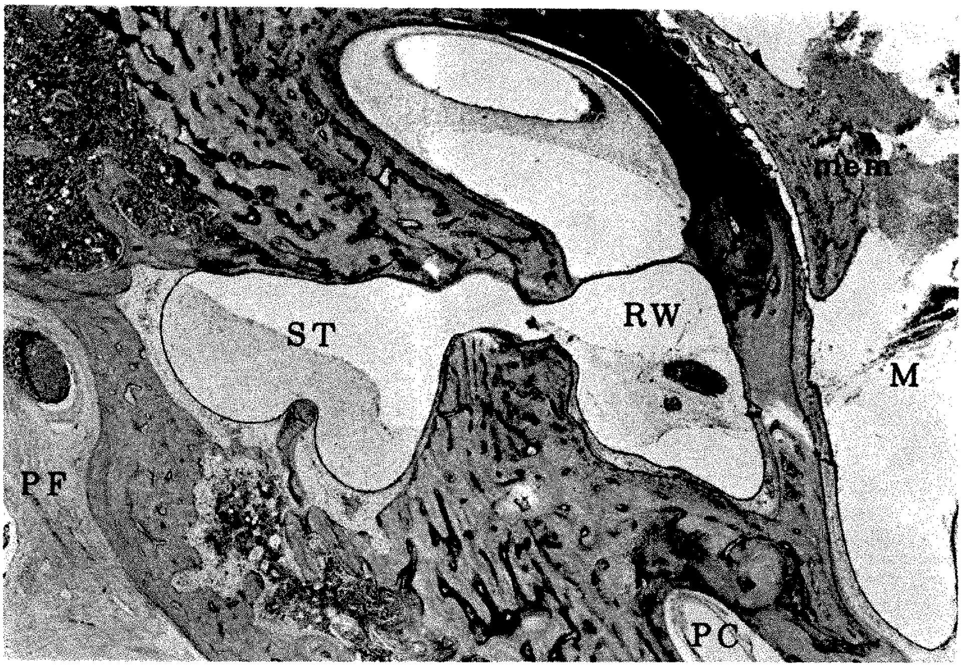

Fig. 2. Photomicrograph at the level of the round window niche (RW). It shows the extension of the sinus tympani (ST) almost to the posterior cranial fossa (PF). M - Middle ear; PC - Posterior canal; mem - Hypertrophic middle ear mucosa. (H & E, X21)

anterior to the epitympanum, and extending downward past the midmodiolar level of the cochlea (Fig. 1). The geniculate ganglion was located within the middle fossa dura anterior to the epitympanum. A few ganglion cells were present in the preganglionic part of the VII nerve. This nerve turned posteriorly, entering a bony channel to cross above the oval window, losing its bony covering for most of the downward extension of its course in the facial canal.

Middle Ear. The middle ear cavity contained a shrunken irregular mass of partially organized mesenchymal tissue and scattered groups of inflammatory cells. The mucosa showed increased vascularity. The pneumatization of the middle ear, extensive around the facial canal, also penetrated the bony loop of the horizontal canal; extending downward and medially from the round window niche, the sinus tympani was unusually extensive[25] and reached almost to the posterior cranial fossa (Fig. 2). The heads of the malleus and incus showed an incomplete development of their joint (Fig. 3). The stapes was present and normal.

Labyrinthine Capsule. Ossification of the enchondral layer of the capsule was abnormally advanced almost to completion. The normal number of coils was present in the cochlea. The middle cranial fossa extended below and anterior to the midmodiolar level of the

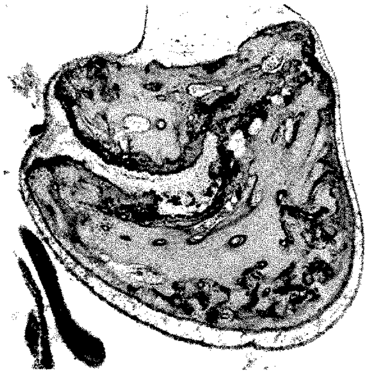

Fig. 3. Heads of malleus and incus, showing an incomplete development of the joint. (H & E)

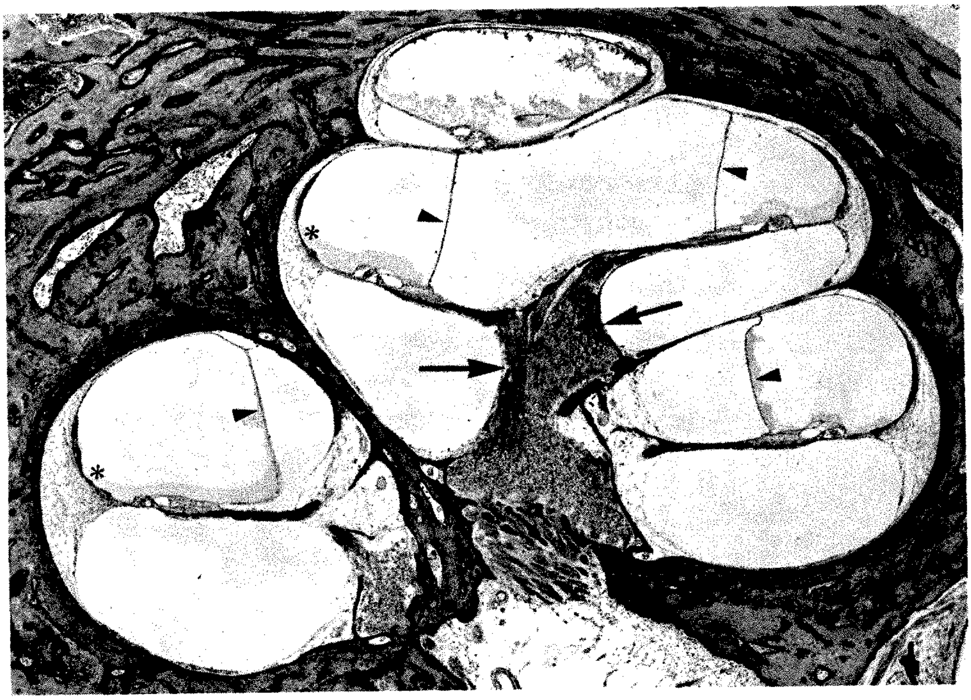

Fig. 4. Cochlea at paramodiolar level, showing an abnormally thin bony framework (arrows), a diffuse hydrops of the cochlear duct (arrow heads) and partial degeneration of the stria vascularis (*). (H & E, X28)

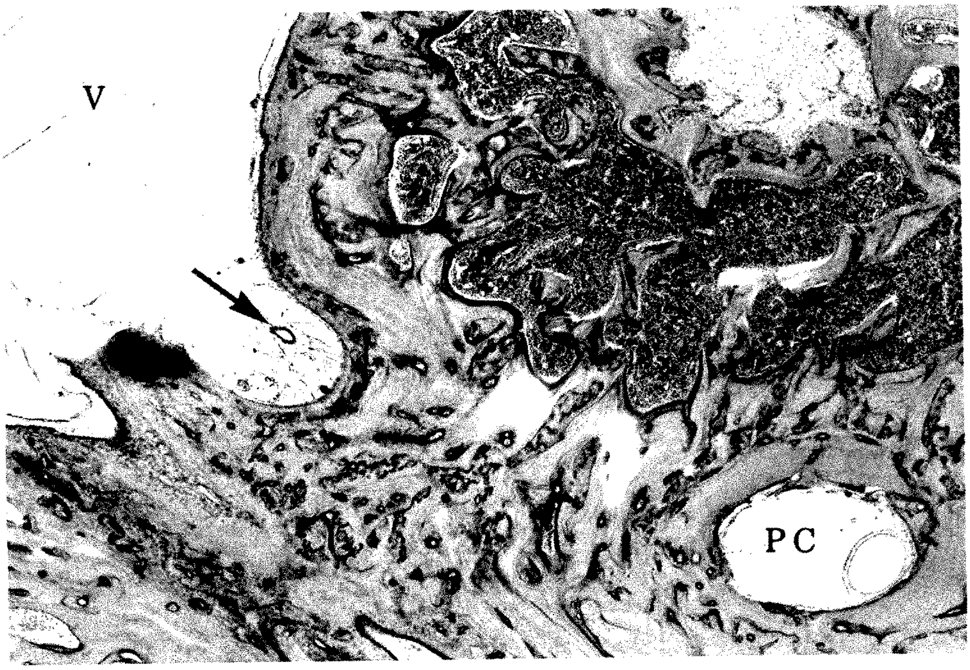

Fig. 5. Section of the vestibule (V) at the level of the common crus and the posterior canal (PC). The vestige of the incomplete membranous common crus is indicated by the arrow. (H & E)

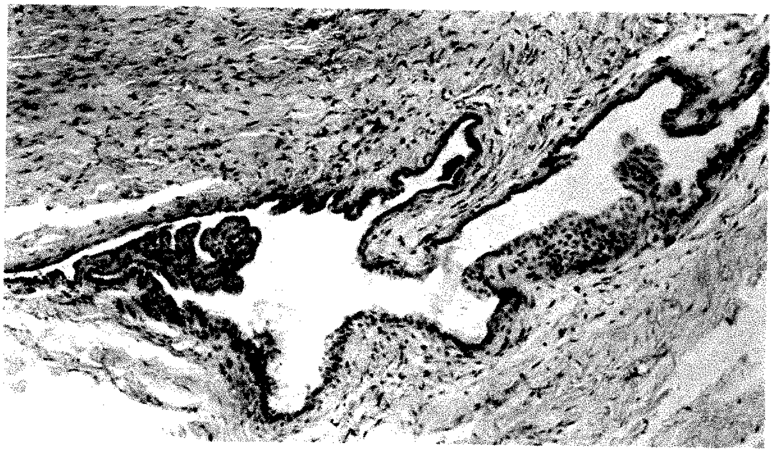

Fig. 6. Convoluted portion of the endolymphatic sac located within the dura. (H & E)

cochlea. An abnormally thin bony framework was evident in the modiolus above the basal coil, but the cochlear partitions were present (Fig. 4). There was no apparent degeneration of the cochlear ganglion which appears to have a normal population. A moderate but diffuse hydrops of the cochlear duct (Fig. 4) and moderate hydrops of the saccule were evident. The stria vascularis showed partial degeneration in the upper part of the apical coil, with a deficiency present in the lower portions of the stria in the basal coil, including the spiral prominence. The organ of Corti, the tectorial membrane and the spiral ligament appeared normal (Fig. 4).

Vestibular System. According to the appearance of the utricle, saccule and three canals, the development of the sense organs was essentially normal. The common crus consisted of only a small cord as a vestige of an endolymphatic canal (Fig. 5). The perilymphatic space was slightly reduced and contained only a few connective tissue strands. The endolymphatic aqueduct was abnormally high in origin and lacked a medial dilatation within the bony capsule. The sac showed convoluted epithelial walls located entirely within the dura (Fig. 6). The cochlear aqueduct contained a bony channel slightly larger than usual, the lumen apparently filled by arachnoid mesh, a small vascular channel, and a core of endothelial-like cells (Fig. 7).

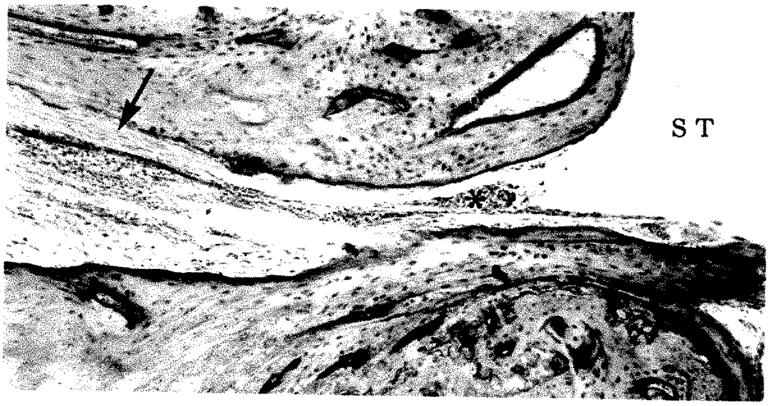

Fig. 7. Section at the level of the orifice of the cochlear aqueduct which is lined by arachnoid mesh (arrow) and endothelial-like cells (*). ST - Scala tympani. (H & E)

LEFT EAR

The block was partially damaged by the saw in removal.

Middle Ear. The overall relationship of middle ear space, middle cranial fossa, geniculate ganglion and labyrinthine capsule was similar to that observed on the right side.

The heads of the malleus and incus were cartilaginous and demonstrated some slight bony fusion in the upper portions. Remnants of infected mesenchymal tissue, partly fibrosed, had remained in the middle ear space.

The labyrinthine capsule was advanced in development. Both the pneumatization of the middle ear and the position of the facial nerve were similar to those on the right.

Cochlea. The number of coils was normal. The bony modiolus was deficient in development, but population of neural elements was similar to that on the right. The cochlear duct was moderately dilated. The stria vascularis, organ of Corti and tectorial membrane appeared normal.

Vestibular System. The structures were also damaged by the saw in removal of the specimen. The endolymphatic common crus showed a lack of development similar to that on the right side. The sense organs were well developed. The convoluted part of the endolymphatic duct was located in the dura of the posterior fossa. The cochlear aqueduct appeared similar to that on the right side.

SUMMARY OF PATHOLOGICAL FINDINGS

The auricles were low-set with poorly developed lobules. The external canals were constricted. However, the eardrums were normal. The incudomalleolar joint was incompletely developed bilaterally. The middle cranial fossae extended abnormally downward between the upper part of the labyrinthine capsule with its contents, and the outer wall of the cranial cavity. This lowered position of the middle cranial fossae thereby corresponded to the lowered position of the external auditory canals and auricles with resulting distortion of the middle ear spaces.

The pneumatization of the posterior and inferior parts of the middle ear showed abnormally extensive development. Air spaces were present around the facial nerve, through the loop of the horizontal canal, and extended medially downward from the niche of the round window to border on the thin wall of posterior cranial fossa.

The cochleas were of normal length but showed a poorly developed bony modiolus above the basal coil. Moderate hydrops of the cochlear duct and saccule was present bilaterally. Sensory elements appeared normal and neural elements filled the spaces in the modiolus. The lower third of the stria was partially degenerated in the apical and basal coils. Except for postmortem changes, the sense organs of the vestibular system appeared normal.

The common crus of the superior and posterior semicircular endolymphatic canals was represented only by a small strand of tissue. The endolymphatic ducts were present bilaterally. The dilated rugose portions of the ducts were located in the dura of the posterior cranial fossa and were well-developed. The cochlear aqueduct appeared larger than usual, but the lumen seemed filled by a fairly dense extension of dural tissue, a small vessel, and a cord-like extension of endothelial-like cells.

DISCUSSION

Most malformations of the auricle, the external meatus, eardrum and ossicular chain are the result of disturbances in the development of the posterior ends of the first and second branchial arches, their adjacent structures and the first branchial pouch and cleft.[19-21]

The presence of low-set or incompletely developed auricles is often accompanied by preauricular pits. These features, when associated with constriction or atresia of the canal, have frequently been accompanied by abnormalities of the eardrum, ossicular chain and the middle ear spaces, with resulting impairment of conduction of sound.

The causes for impaired conduction of sound have been partially accessible for investigation by clinical and x-ray examination, middle ear surgical investigation, or by gross postmortem observation.

About one-third of such cases have been associated with varying degrees of nerve deafness;[19-21] the basis for which, usually requires histopathological examination, and has seldom been determined.

The philogenetically older vestibular system has been considered less susceptible to errors in development than the auditory sense organ. Any maldevelopment of the vestibular system, if limited to membranous parts, has usually not been suspected on clinical observation. However, recent histopathological reports suggest that vestibular anomalies are in fact frequent.[1,19-24] The semicircular canals are developed in the 9-17 mm stage of embryonic gestation, corresponding to the sixth to seventh week. Any gross defects in development are already present at that stage.[26] Dedifferentiation of the primitive precartilaginous tissue to form the perilymphatic space develops around the primitive canal and is therefore dependent upon the presence of the membranous canal system.

The common crus in the present case, although consisting only of a nonpatent strand of tissue, was apparently sufficient to induce development of a patent although reduced perilymphatic space within a bony common crus.

The abnormalities of the auditory system in this case consisted of a minor degree of distortion of the ossicular chain and an incomplete incudomalleolar joint. The cochlea was normal in length with a modiolus which appeared abnormally thin above the basal coil but was fully occupied by neural elements.

The moderate hydrops of the cochlea and saccule and the deficiencies in the stria vascularis are an indication for some degree of impairment of sensorineural function. The existence of the defective stria vascularis and the cochleosaccular hydrops is not explained, although they may be interrelated. The hydrops in this instance differs from that frequently seen in the cochleosaccular type of congenital anomaly described by Scheibe.[27,28]

The degenerative changes in the tectorial membrane and organ of Corti usually seen in the Scheibe type were absent here. Scheibe also called attention to the absence of any abnormalities of the bony structure in his original cases. This case also does not present the main features described by Mondini[29] of deficient cochlear partitions and enlarged endolymphatic duct and sac. However, the designation "Mondini-type of deafness" has sometimes been applied to combined anomalies of the cochlear and vestibular systems.[23]

The presence of a well-developed endolymphatic duct with the dilated portion with rugose epithelium situated beneath the dura seems to exclude obstruction of the duct as a cause for the hydrops in this instance.

Regarding the case in general, abnormalities such as the low-grade middle ear inflammation, the acute renal suppuration and the depressed ability of the patient to produce proper lymphocytic responses to induced stimulation all appear to be expressions of an overall immunosuppression. Such factors were essential in the formulation of the final general diagnosis of immunodeficiency disease with ectodermal dysplasias and short-limbed dwarfism.

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TREATMENT OF INFANTILE SUBGLOTTIC HEMANGIOMA WITH RADIOACTIVE GOLD GRAIN

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SUMMARY — Congenital subglottic hemangioma causes life-threatening airway obstruction during the first few months of life. The mortality rate of recognized and untreated cases justifies active treatment, and although radiation therapy is currently most favored, it carries a risk of inducing malignant change in the thyroid gland later in life. A series of 11 patients with laryngeal hemangiomata is reported, conventional radiotherapy was utilized in the first seven patients, and placement of a radioactive gold grain directly into the lesion was used in the last four patients. This technique offers maximal tumor dose with minimal thyroid gland irradiation compared to treatment by conventional radiotherapy, and its successful use in these four patients is reported as worthy of further trial.

Cutaneous and subcutaneous hemangioma of the head and neck region in infancy are relatively common and the accepted management is to await spontaneous regression. However a localized laryngeal hemangioma may occur with or without an associated cutaneous lesion. A review of the literature[1-4] reveals a high mortality for unrecognized, untreated and even treated cases, and when such a malformation causes life-threatening airway obstruction active treatment is justified.

In infants the lesion is usually localized to the subglottic region on one side with a characteristic appearance (Fig. 1). The hemangioma is sessile, soft and compressible with a pinkish or bluish color and not well delineated from the surrounding tissues.

There have been numerous reports in the literature in the last 30 years with particular reference to the method of treatment. Radiation therapy is now favored by many authorities but carries the risk of inducing malignant change in the thyroid gland later in life. It is not known how great this risk is.[5,6]

Four children have been treated recently at the Royal Alexandra Hospital for Children, Sydney by placing a radioactive gold grain in the subglottic hemangioma. These four patients, together with seven others previously treated by conventional radiotherapy, are the subjects of this report.

CASE MATERIAL

The onset of symptoms (Table 1) was between birth and eight weeks of age. In two patients the diagnosis was not made until one year of age. There were seven females and four males. Five of the 11 cases had coexistent superficial hemangiomata. In nine patients the hemangioma was localized in the subglottic region and in one of these patients bilateral lesions were present. In the remaining two patients the hemangioma was generalized in the larynx.

One patient died about six weeks after radiation, while the tracheotomy was still in place, but the cause of death was unexplained at autopsy. The hemangioma had shrunk to a negligible size.

Tracheotomy was necessary or desirable in all but one patient either to treat acute or progressive airway obstruction or to allow therapy to be administered safely and satisfactorily.

Clinical Features. The infant usually presents at a few weeks of age with inspiratory stridor, the severity depending upon the size, the presence of infection and inflammation, swelling, and

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From the Royal Alexandra Hospital for Children, Sydney, Australia.

TABLE 1. LARYNGEAL HEMANGIOMA IN INFANTS

Case	*Onset (wk)*	*Diagnosis (wk)*	*Skin Lesions*	*Site*	*Therapy*	*Comment*
1	8	10	Yes	L. Sub.	X-ray dose 2	Steroids not effective
2	7	8	Yes	R. Dif.	X-ray	—
3	5	7	Yes	L. Sub.	X-ray	Unexplained sudden death
4	8	10	Yes	L. Sub.	X-ray	No tracheotomy
5	8	16	No	R. Sub.	X-ray	Additional piecemeal removal
6	1	5	Yes	Gen. Dif.	X-ray	Steroids not effective
7	6	53	No	L. Sub.	X-ray	Delayed diagnosis
8	2	3	No	L. Sub.	Gold grain	Intubation. Delayed cure
9	4	16	No	Bil. Sub.	Gold grain	Additional piecemeal removal
10	Birth	52	No	L. Sub.	Gold grain	Intubation. Delayed cure
11	8	14	No	R. Sub.	Gold grain	—

L. - Left; Sub. - Subglottic; R. - Right; Dif. - Diffuse; Gen. - Generalized; Bil. - Bilateral.

the degree of vascular engorgement and congestion of the hemangioma. There may be attacks of so-called "croup," sometimes associated with a harsh cough, like "the bark of a dog." There may be periods of intermittent remission and exacerbation, or the stridor may become persistent as progressive laryngeal obstruction occurs.

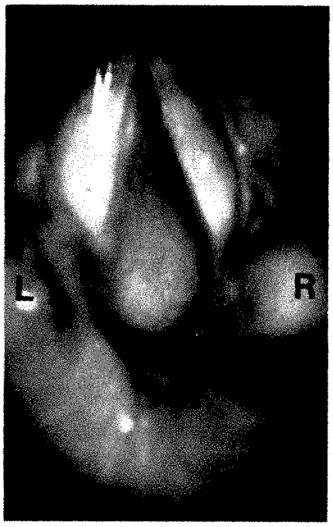

Fig. 1. Typical subglottic hemangioma, under the left vocal cord with marked narrowing of the glottic airway.

A lateral upper airway x-ray or xeroradiogram may show changes consistent with subglottic soft tissue swelling or a somewhat circumscribed and localized soft tissue mass.

The diagnosis is suspected by being aware of the condition and a final diagnosis is made at direct endoscopic examination under general anesthetic; the appearance alone is sufficient for an experienced observer to make a confident diagnosis. Biopsy is not usually necessary but may be performed with little bleeding if the diagnosis is uncertain or where, as a consequence of surgical piecemeal removal, tumor is available for histological study.*

Treatment. Various modes of treatment have been advocated.

Tracheotomy and "watchful expectancy" means acceptance of the tracheotomy tube, possibly for a number of years, with its attendant dangers and problems in communication. Doermann *et al*[1] reviewed 15 cases collected from the literature and four out of five patients died when managed by this so-called conservative treatment. Tefft's[4] review also revealed a high mortality.

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*Patient 1 and Patient 2 were biopsied by the author and thus were histologically proven. Patient 3, who came to postmortem, had a small nodule of residual hemangioma histologically examined and proven. Patients 5 and 9 were proven when the specimens from piecemeal removal were examined histologically. Patient 7 was initially seen at another hospital and biopsied there and histologically proven. Therefore 6 of the 11 patients were histologically proven, and 5 had the diagnosis made presumptively from the appearance seen at laryngoscopy.

Surgical removal[7,8] either by external surgery or endolaryngeal surgery is technically difficult in an infant and trauma and subsequent scarring may produce an acquired subglottic stenosis.

Pierce[7] advocated the injection of sclerosing fluids and has reported encouraging results; but we have been concerned about possible fibrous reaction and stenosis and have not used this technique.

Steroid therapy, based on the apparent response of other head and neck hemangiomatous lesions has proved ineffective in two of our patients.

Intermittent intubation over a prolonged period has been used[10] but it sentences the patient to long periods of hospitalization and the patient cannot vocalize. Such intubation caused fibrosis in the subglottic region in two patients in this series thereby making later irradiation therapy less effective. Our experience does not support this means of management.

Laser beam irradiation has yet to be thoroughly evaluated and may prove to be a satisfactory means of treatment.

Radiation therapy is currently most favored. In 1961 Ferguson and Flake[2] recorded their series of 17 cases treated by external x-ray therapy with only one death. In a review of the literature up to that time they found that 50% of the 24 recorded cases had been fatal. External irradiation has been most commonly used and this was our practice until Holborow and Mott[11] reported the use of a radioactive gold grain in 1972. A similar technique has been used in the last four patients in our series.

The gold grain is a small cylinder about 2.5 mm long and 0.8 mm in diameter. We use a dose of one millicurie and the half-life of the radioactive gold grain is 4.7 days. This gives maximum tumor dose and yet the dose to the thyroid gland is minimized. The dose 1 mm from the center of the grain is 22,000 rads and the dose 1 cm from the center of the grain is a little over 200 rads.

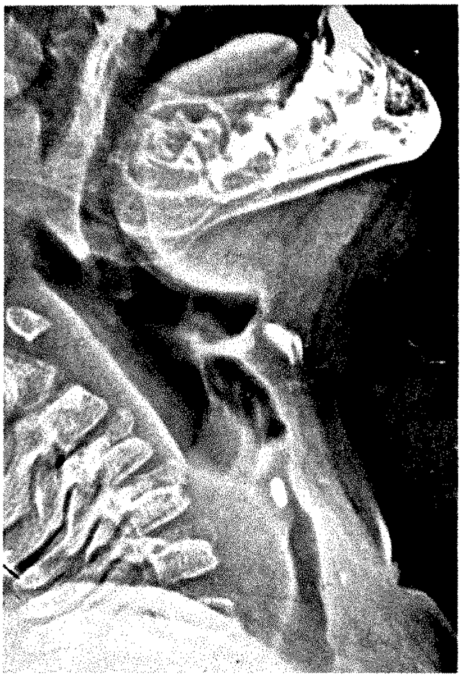

Fig. 2. Xeroradiogram showing grain in the subglottic hemangioma.

Using the endolaryngeal microsurgical technique the grain is inserted into a pocket just below and medial to the edge of the true cord so that the grain enters the center of the hemangioma. There is very little bleeding. The position of the grain is immediately checked by x-ray or xeroradiogram (Fig. 2). It is necessary to wait at least eight weeks for any worthwhile effect of the radiation and removal of the tracheotomy tube is usually achieved within 12 weeks but varies from patient to patient. Some hemangioma always remains.

There are other factors which affect the success of therapy. The patients who had already had intermittent and prolonged intubation showed evidence of superficial fibrosis in the subglottic region and this limits the response. Also interconnection with coexisting subcutaneous or deeper hemangiomata in the neck seems to affect the response as does the dose of radiation therapy and the age at which it is carried out.

If radiation alone does not achieve the desired results in three or four months, either more irradiation may be given (Patient 1) or piecemeal microsurgical removal may be undertaken (Patient 5 and Patient 9).[*]

CONCLUSION

Because of the reported death rate when the lesion is not treated, active treatment is justified. The response to irradiation therapy has been fairly reliable, all patients showing worthwhile response although individual dosage is difficult to estimate.

Use of a radioactive gold grain is reported as worthy of further trial to limit unnecessary irradiation of the thyroid gland and lessen the subsequent possibility of malignant change.

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[*] The following is a follow-up on the four patients in whom a radioactive gold grain was used: The longest follow-up was two years and three months. Follow-up has been careful with regular reviews and there has been no recurrence of the hemangioma and so far no sign of untoward effects from the radiation treatment. All patients are seen regularly both by the author and by a pediatric endocrinologist.

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STUDIES ON COCHLEAR AQUEDUCT PATENCY

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SUMMARY — Complex studies on the patency of the cochlear aqueduct were made on 250 human cadavers and the temporal bones isolated from these, using a chemical method (staining reaction) as well as filling the aqueduct with fluid plastics and exposing the whole of its course under an operating microscope. The disappearance of patency in the cochlear aqueduct is a progressive phenomenon reflecting the biological process of aging in the organism. Patency of the cochlear aqueduct renders possible a two-way spread of infection from the cerebrospinal fluid (CSF) to the inner ear and *vice versa*, CSF otorrhea, and sudden sensorineural hearing impairment through rises in CSF pressure, while in the absence of patency, the accumulation of harmful products of metabolism in the perilymph has a deleterious effect on the sensory elements of the inner ear.

The history of studies on the cochlear aqueduct already reaches back nearly 300 years, beginning from the anatomical discoveries of DuVerney in 1683,[1] Pacchoni in 1721 cited in Karbowski,[2] and Cotugno in 1774.[3] Many studies on the role of the cochlear aqueduct, some still in progress, have established the descriptive and comparative anatomy as well as the histology of the organ, although there are markedly divergent opinions on the subject. There is, however, still much to be elucidated in the physiological role of the cochlear aqueduct, as regards the interdependence of the environments of the cerebrospinal fluid (CSF) and the perilymph.

Opportunities of studying the patency of the cochlear aqueduct in the human are of necessity limited. Investigations in short series of cases have been made by Karbowski,[2] Karlefors,[4] Winckler,[5] Palva and Dammert,[6] and Ritter and Lawrence.[7] Suzuki[8] carried out studies on 68 human cadavers about 12 hours after death. He injected methylene blue through the round window into the scala tympani, and found that in 42% of cases, the cochlear aqueduct was patent at a pressure of less than 30 ml of a mercury column. The aqueduct was patent in 75% of cases under 21 years of age, but only in 32% of the elderly.

METHODS AND MATERIALS

The fundamental aim of the experimental studies now reported was to estimate the patency of the cochlear aqueduct during the whole ontogeny of the human, from fetal life to advanced age. Composite experiments on cadavers and isolated preparations of the temporal bones were carried out on 250 deceased persons of both sexes, ranging in age from five months of fetal life to 95 years (Table 1).

The whole series of studies consisted of:

1. Indirect experiments on human cadavers, using chemical staining reactions;
2. Direct experiments on temporal bones isolated from cadavers on which investigations *in situ* had already been carried out, using chemical staining reactions;
3. Experiments involved in filling the lumen of the cochlear aqueduct with colored fluid plastic substances as well as exposing under an operating microscope the whole of the aqueduct together with the basal turn or the superior turns of the cochlea as well as the round window; these experiments were made on the same temporal bones on which chemical tests had previously been made;
4. Black and white or colored photographic documentation of all the preparations with the cochlear aqueduct filled with latex or microfill, and exposed.

Indirect experiments were made on human cadavers of both sexes and various ages, 12 to 24 hours after death, using the chemical staining reaction between salicylic acid and ferric trichloride ($FeCl_3$). Salicylic acid was used in the form of 2% salicylic alcohol (a colorless fluid) and $FeCl_3$ in the form of a 5% aqueous solution (a yellowish fluid). Indirect experi-

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TABLE 1. DISTRIBUTION OF NUMBER OF EXPERIMENTS IN PARTICULAR STAGES OF DEVELOPMENT

			No. of Cases	
	Stages of Development		*Subgroups*	*Groups*
I	Fetal stage	Fetuses from immature and premature births between 5 and 8 months of fetal life	25	50
		Neonates born at term (9 months of fetal life)	25	
II	Stage of growth and maturity	Younger children 2 wk to 3 yr	25	50
		Older children 4-16 yr	25	
III	Stage of greatest biological activity	20-29 yr	25	50
		30-39 yr	25	
IV	Stage of stabilization and beginning of biological regression	40-49 yr	25	50
		50-59 yr	25	
V	Stage of aging and senile involution	60-75 yr	25	50
		76-95 yr	25	

mentation on cadavers consisted in 1) aural surgery in order to expose the round window in the inner ear, to interrupt the continuity of the secondary tympanic membrane, and to place a pad of cotton wool soaked in $FeCl_3$ solution in the round window; 2) suboccipital puncture by Eskuchen's indirect method in order to introduce as large a volume as possible of 2% salicylic alcohol (from 50 ml in fetuses to 250 ml in adults) into the region of the intracranial cisterns and CSF spaces. In cases when $FeCl_3$ flowed through the cochlear aqueduct a more or less intensive violet staining reaction was observed in the round window.

In experiments on isolated temporal bones each preparation included on the abneural side the sigmoid fossa or its anterior edge, a longitudinal cross section of the jugular fossa, the jugular foramen, the inferior petrosal sinus, and the channel of the internal carotid artery. Preparations dissected out in such a manner ensured free and easy access to the bony infundibulum of the external aperture of the cochlear aqueduct along its long axis. On the side of the external auditory meatus the material dissected out was prepared in such a manner that the round window was in the center of the field of vision, and at the same time there was a good view of the hypotympanum, the tympanic sinus and the oval window. The infundibulum of the external aperture of the aqueduct was localized under the microscope, and then the unnecessary soft parts belonging to the petrous ganglion of the glossopharyngeal nerve were removed, and the meningeal folds arranged in a natural manner by the walls of the infundibulum. In this way a direct view into the external aperture of the cochlear aqueduct was obtained. The round window was closed with a pad of cotton wool soaked in a solution of $FeCl_3$. A blunt-ended needle of suitable caliber attached to a pressure syringe with 2% salicylic alcohol was introduced into the external aperture of the cochlear aqueduct. The preparation of the external auditory meatus was fixed in

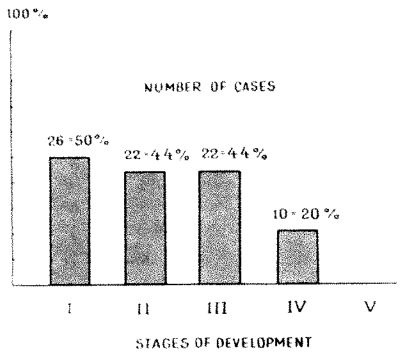

Fig. 1. Indirect tests of cochlear aqueduct patency in particular stages of development.

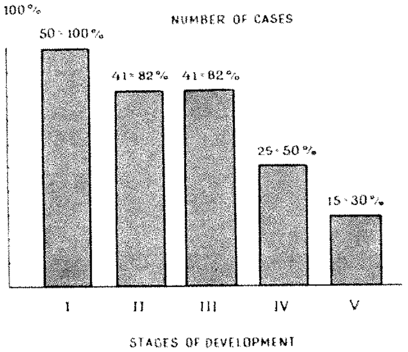

Fig. 2. Direct tests of cochlear aqueduct patency in particular stages of development.

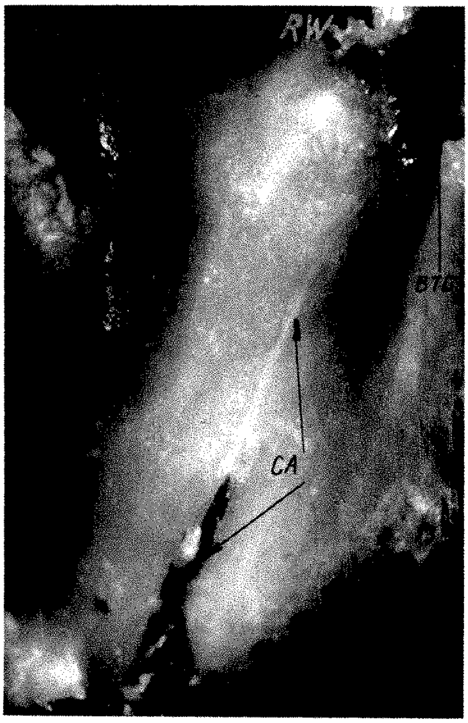

Fig. 3. Obstructed cochlear aqueduct in adult: plastic fills the initial section of the aqueduct and the further section is visible in the form of a white streak reaching the region of the internal aperture. RW - Round window; BTC - Basal turn of cochlea; CA - Cochlear aqueduct.

an upright position and the fluid was introduced into the external aperture of the aqueduct. When the aqueduct was patent, a more or less intensive staining reaction was observed on the cotton wool pad closing the round window, and in the hypotympanum.

In order to check the correctness and reliability of the tests of cochlear aqueduct patency when the chemical staining reaction between $FeCl_3$ and 2% salicylic alcohol was used in all the 250 preparations of isolated temporal bones, the aqueduct was filled with microfill or latex. Orange and brown microfill or white latex was used with an addition of original stains (red, blue and yellow). Under an operating microscope the whole cochlear aqueduct was exposed on the inferior surface of the petrous bone, using an electric drill. On exposure, the color of the stained plastic gave information on the interior of the aqueduct. The bony canal of the aqueduct itself was not opened, leaving a delicate external osseous lamina or the internal periosteum of the aqueduct. The basal turn of the cochlea with the internal aperture of the aqueduct and the middle and apical turns were opened. The round window was exposed from below.

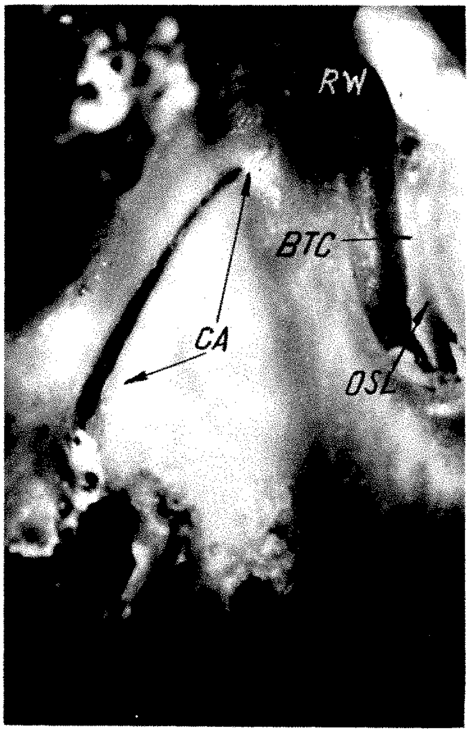

Fig. 4. Obstructed cochlear aqueduct in adult: almost the whole aqueduct is filled with plastic, a short section in the form of a white streak is seen before the internal aperture. OSL - Osseus spiral lamina.

RESULTS

Indirect experiments on cadavers showed that fluid flowed from the subarachnoid space to the inner ear (through the cochlear aqueduct) in 80 out of 250 cases, *i.e.*, in 32% of cases. The distribution of these cases among the particular stages of development is shown in Figure 1. Most were found in fetuses and neonates, the numbers were equal in children and adolescents, while there was a marked fall between the ages of 40 and 60, and a complete absence in the aged (Stage V).

In direct tests on isolated temporal bones, the cochlear aqueduct was found to be patent in 172 out of 250 cases, *i.e.*, in 68% of cases. The distribution of these cases among the particular stages of development is shown in Figure 2. The proportions of cases of cochlear aqueduct patency in particular stages of development were similar to

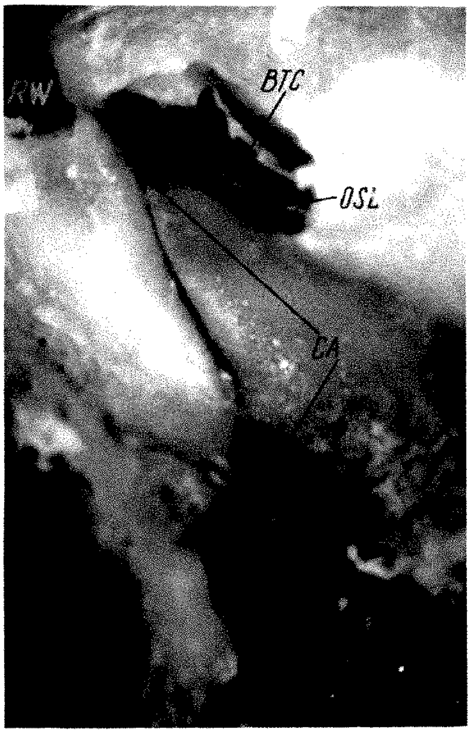

Fig. 5. Younger child: plastic fills part of the basal turn near the internal aperture.

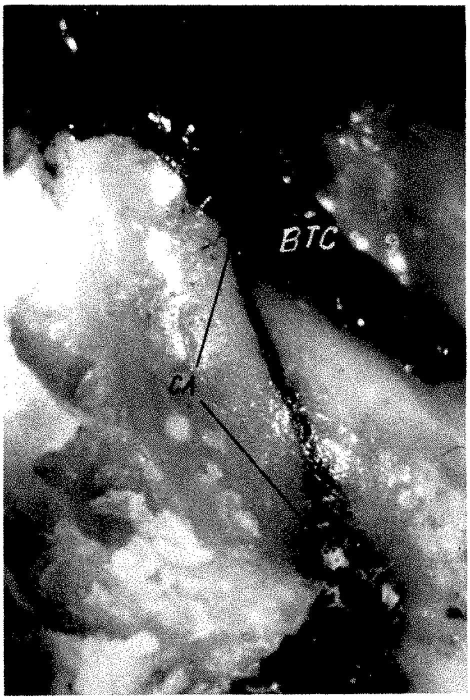

Fig. 6. Adult: plastic fills the whole basal turn.

those in the indirect experiments on cadavers: 100% of cases of patency in fetuses and neonates, equal percentages in children and adolescents, and a marked lessening of the percentage in the older age groups. Absence of patency in the aqueduct was found at earliest in the fifth week of life, while the latest age when patency still existed was 89 years.

Experimentation with microfill and latex fully confirmed the quantitative and qualitative results of the direct tests of cochlear aqueduct patency in which the chemical staining reaction between $FeCl_3$ and a 2% salicylic alcohol was used.

In impatent preparations, fluid plastic filled the long section of the aqueduct from the side of the external aperture in different ways, but never reached the internal aperture.

In cases of obstruction two morphological pictures were observed:

1. Beyond that part of the aqueduct, differing in length, which was filled with plastic, a further section of the bony canal of the aqueduct can be seen under the microscope in the form of a white or yellowish streak reaching up the internal aperture. It may be assumed that in these cases the impatency of the aqueduct depended on the structure, thickness and arrangement of the soft tissues in the region of the bony canal (Figs. 3 and 4).

2. Beyond that part of the aqueduct filled with plastic, the further section of the bony canal of the aqueduct is not evident; in these cases impatency was probably caused by obliteration, the atrophy of the bony canal.

On the other hand, in every preparation in which patency was ascertained by chemical testing, microfill or latex was found in the whole of the cochlear aqueduct from the external to the internal aperture, in some cases also filling the inner ear to various degrees.

In patent preparations three main groups were found, differing in the degree to which microfill or latex penetrated into the region of the labyrinth:

1. The plastic fills the whole cochlear aqueduct including the infundibulum of the internal aperture, without penetrating the basal turn of the cochlea;
2. Beyond the aqueduct the plastic is found in the basal turn of the cochlea (Figs. 5 and 6);
3. The plastic densely fills the basal turn of the cochlea (or the superior turns) as well as the rim of the round window or the spaces on the exterior of the round window.

Marked individual differences were found in the course, length and thickness of the cochlear aqueduct.*

DISCUSSION

Composite investigations demonstrated quantitative differences between the results of experimentation on cadavers and on isolated preparations of the temporal bones. Though a closer approximation to natural intravital conditions was achieved in the experiments on cadavers, yet the possibilities of penetrating the inner ear (through the patent cochlear aqueduct) with substances introduced into the intracranial cisterns and CSF spaces are worse than when these substances are forced into the external aperture of the aqueduct. This is certainly due to the presence of CSF in these spaces, since this renders it difficult for the 2% salicylic alcohol introduced into the cisterna magna of the brain to reach the cochlear aqueduct. In spite of the differences between indirect and direct testing, similar quantitative proportions were observed between the particular stages of development, namely the diminishing numbers of cases with patent cochlear aqueducts in successive stages. In both experiments qualitative differences were also ascertained. In studies on cadavers in the fetal stage and early childhood, the staining reaction in the round window was observed before creating maximal hypertension in the CSF cisterns. The staining reaction was usually very intense, the stain often spread beyond the region of the round window closed with cotton wool into the hypotympanum, and the passage of the fluid through the aqueduct took a comparatively long time. In adults, on the contrary, the flow of the fluid through the cochlear aqueduct was obtained only after creating maximal hypertension in the CSF cisterns, and the staining reaction in the round window was on the average weaker and lasted for a shorter time. In studies on isolated temporal bones it was found that the proportions between aqueduct patency defined as excellent, good, and poor, undergo changes with age, and finally the last predominate.

Obliteration of the patency of the cochlear aqueduct is a progressive phenomenon reflecting the process of aging in the organism. This process consists in the gradual extension of the length of the aqueduct and a decrease in its breadth, which has a fundamental effect on the patency of the free lumen of the aqueduct, filled to various degrees with soft tissues. There are two critical factors in the process of obliteration of cochlear aqueduct patency. The first occurs on the borderline between fetal development, when the aqueduct is always patent, and the first week after birth, when cases of impatency may already be encountered. This first crisis is, so to speak, an abridged version of the phylogenic development. In the conditions of intrauterine development in a fluid environment the cochlear aqueduct, always patent, may serve for the transmission of changes in the CSF pressure to the organ of equilibrium. From the time of leaving the fluid environment, as the proprioreceptive stimuli develop and an upright position is assumed, this function of the aqueduct ceases to be of fundamental importance. The second crisis occurs in Stage IV, when biological regression begins and a significant rise in the number of cases of aqueduct impatency is observed.

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*The bank of 250 temporal bones with the cochlear aqueduct filled with microfill or latex and exposed under an operating microscope is deposited in the Department of Otolaryngology in the Cracov Academy of Medicine.

The analogy of postmortem experiments to that in the living is very distant. However, the results obtained enable the following generalizations to be formulated as probable.

The CSF spaces form a supplementary cistern for the perilymph until the time when the process of obliteration of cochlear aqueduct patency begins, though this does not appear in all cases. The CSF may therefore be considered as one of the sources, if not the only source, of origin of the perilymph.

It may be assumed as probable that the obliteration of the patency of the cochlear aqueduct is not without effect on the sensory functioning of the inner ear. The obliteration developing with age may lead to a gradual accumulation of products of tissue metabolism in the perilymph, and these may have a deleterious effect on the sensory cells of the inner ear. The process of obliteration of cochlear aqueduct patency may therefore cause progressive hearing impairment of the cochlear type earlier than is usual.

The correlations between the perilymph and the CSF are based in children, adolescents and young subjects on communication through the cochlear aqueduct, usually patent in these stages of development. This affects the aural CSF discharges occurring spontaneously in children, or after operations for opening the perilymph spaces in otosclerosis[9-12] and Ménière's disease in adults. There are similar possibilities in purulent meningitis, in the course of acute, viral, or bacterial otitis media, when the morbid process spreads to the cochlea through the secondary tympanic membrane of the round window, and in cases after stapedectomy, if the fistula in the round window does not close.[13-16] The spread of infection through the patent cochlear aqueduct should also be borne in mind in cases of bilateral perceptive deafness in children and adolescents, in the course of purulent meningitis as a result of retrograde labyrinthitis.[17,18]

It is also probable that some injuries to hearing are consequent upon sudden and considerable rises in CSF pressure transmitted to the inner ear through the cochlear aqueduct and leading to transient or permanent injury to the cells in the organ of Corti. This may result in sudden deafness of unknown origin, and also certain forms of Ménière's disease. According to this conception, the essential therapy in similar morbid conditions is to apply means of rapidly and effectively lowering the CSF pressure[19] and surgical treatment for the closure of fistulas in the oval and round windows draining the perilymph.[20]

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NINCDS NOTES*

SPECIAL NOTE TO NINCDS GRANTEES

All papers reporting or based upon NIH supported work must carry a notation giving credit to the funding Institute and the grant number. The notation is necessary both to meet the administrative, congressional reporting, and program analysis needs of the Institutes, and to provide the National Library of Medicine with essential bibliographic and indexing keys. Grantees are urged to stress this requirement in communications with their publishers.

TWO YEAR ASSOCIATE POSITIONS AT NIH

Applications are now being accepted for clinical, research, and staff associate appointments to begin July 1979 and 1980 at NIH. Approximately 150 associates are selected each year for these two-year positions. Training and experience in virtually all areas of clinical and preclinical biomedical research are offered by the 12 participating Institutes.

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Deadline for receipt of applications is February 15, 1978. Interviews will be conducted April 17-28, 1978. Final selections are to be made in May by a matching process in which the candidate's preferences are matched with the Institute's preferences. To request application forms and a detailed catalog describing the program write or call collect: NIH Associate Program, National Institutes of Health, Building 10, Room IN-238A, Bethesda, MD 20014. Telephone: (314) 496-2427.

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The Internal Revenue Service has ruled that National Research Service Awards are made primarily for the benefit of the grantor and are accordingly not excludable from gross income as fellowships. (IRS Bulletin No. 1977-36, dated September 6, 1977.) The ruling is currently being studied by a Congressional Committee for possible legislative relief.

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TREATMENT OF SUDDEN DEAFNESS WITH SODIUM SALTS OF TRIIODOBENZOIC ACID DERIVATIVES

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SUMMARY — Twenty-two patients with a complaint of sudden deafness were treated with one or the other of two of the radiopaque contrast media, 9 received daily doses of sodium iothalamate, and 13 were treated similarly with methlyglucamine and sodium iodamide. Four of the first group and eight of the second demonstrated either an effective partial or a complete recovery of hearing function. Those failing to respond were generally classified completely deaf at admission and reported nausea, vomiting, or vertigo at onset of sudden deafness. Treatment with sodium salts of triiodobenzoic acid derivatives, *i.e.*, sodium iothalamate and methylglucamine and sodium iodamide, is judged to be effective in selected cases of sudden deafness.

"Sudden deafness" is a sensorineural deafness of unknown etiology. Various suggested treatments, such as stellate ganglion block or the administration of vasodilator agents, have generally proved disappointing. In 1973, it was found and reported that sudden deafness could be effectively treated by the administration of the radio-contrast medium, methylglucamine and sodium diatrizoate (76% - Urografin®).[1-3] In the present study, we will report our experiences in treating an additional 22 cases of sudden deafness with contrast medium therapy.

METHODS AND MATERIALS

Subjects of this study were 22 patients with the complaint of sudden deafness, seen in Kyushu University Hospitals between August 1974 and August 1976. Of the 22 patients, 11 were male and 11 female. Their ages ranged from 18 to 58 years with an average age of 36.6 years. The time delay between the onset of hearing loss symptoms and admission ranged from 2 to 25 days with an average delay of 6.8 days. Three patients presented with a bilateral hearing loss; ten indicated a unilateral loss in the right ear and the remaining nine showed a unilateral loss in the left ear. On the day of admission, a pretreatment audiogram was taken for each patient. Treatment effects were evaluated from sequential audiograms taken prior to the daily treatment administration. All audiograms were obtained using standard clinical audiometric procedures. Audiometers were calibrated to ISO standards and all audiometry was performed in sound-treated test booths in the Otorhinolaryngology Clinic.

All patients were seen as outpatients daily (except Sundays). Treatment consisted solely of the administration by bolus I.V. injection of one of the radio-contrast media. For the first group of nine patients, sodium iothalamate (80% - Conray-400®) was used at a dosage of 1.60 gm; the remaining 13 patients received methylglucamine and sodium iodamide (80%-Conraxin-H®) in doses of 1.60 gm (except for one of the latter patients with a longer delay, 25 days, between deafness onset and presentation for treatment for whom the dosage was set at 4.0 gm). These initial doses were administered daily for a minimum of four days. Treatment was continued after the first four days at either the same dose for patients demonstrating obvious improvement in that time, or at the increased dose of 16.0 gm for those showing little or no change in their condition at the end of the initial four-day period. If no significant improvement was noted after seven days, the contrast medium therapy was discontinued and the patient was transferred to a program of high-pressure oxygen treatment administered in a hyperbaric whole-body chamber. Otherwise, treatment was continued until the recovery appeared to be either complete or stabilized. Total treatment time ranged from 4 to 16 days with an average of 10.2 days for patients showing recovery.

RESULTS AND DISCUSSION

Initial audiograms from all 22 patients were invariably compatible with a classification of sensorineural deafness. Following the contrast medium therapy in the first group of nine patients, those treated with sodium iothalamate, two showed almost complete recovery and another two, partial recovery of hearing. For the other five, no improvement was noted. The recovery data is sum-

TABLE 1. RESULTS OF TREATMENT WITH SODIUM IOTHALAMATE IN TERMS OF AVERAGE OF SPEECH FREQUENCIES IN dB

Case	*Side*	*Pre-Rx*	*Post-Rx*
1	L	68.3	15.0
2	L	58.3	8.3
3	L	60.0	38.3
4	R	86.7	36.7
	L	25.0	10.0

TABLE 2. RESULTS OF TREATMENT WITH METHYLGLUCAMINE AND SODIUM IODAMIDE IN TERMS OF AVERAGE OF SPEECH FREQUENCIES IN dB

Case	*Side*	*Pre-Rx*	*Post-Rx*
1	R	55.0	15.0
	L	35.0	15.0
2	R	11.7	-3.3
	L	61.7	3.3
3	L	80.0	3.3
4	R	61.7	8.3
5	R	56.7	28.3
6	R	38.3	1.7
7	L	56.7	1.7
8	R	46.7	1.7

marized in Table 1. In the second group of 13, treated with methylglucamine and sodium iodamide, seven recovered to normal and one to near normal thresholds on the audiogram. The remaining five failed to demonstrate any response to the contrast medium therapy. Recovery data for this second group are summarized in Table 2. Sample audiograms are shown in the figures. Figure 1 is for Case 2, Table 1. Figure 2 is for the right ear, and Figure 3 for the left ear of Case 1, Table 2.

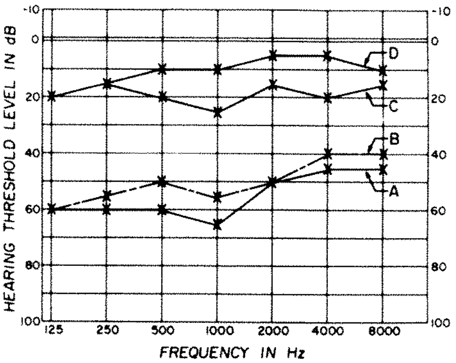

Fig. 1. (Case 2) Audiograms taken: A) before treatment (8-22-74); B) one day after initial treatment (8-23-74); C) after four days (8-26-74); D) after five days (8-27-74). See Table 1.

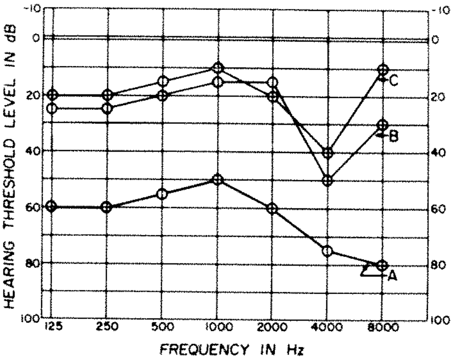

Fig. 2. (Case 1) Right ear audiograms taken: A) before treatment (12-24-74); B) after fourth and final daily treatment (12-28-74); C) one month after final treatment (1-31-75). See Table 2.

In general, it was noted that the patients who did not respond to the contrast medium therapy differed from those who did respond on two counts: 1) they usually reported symptoms of nausea, vomiting, and vertigo associated with the onset of their deafness; 2) they failed to respond to the audiometer at any frequency at the maximum test level available (90 dB HL), *i.e.*, "complete deafness." Only those patients with measurable audiometric thresholds at some frequencies, *i.e.*, "partial deafness," at admission and without symptoms of nausea, vomiting, or vertigo accompanying the onset of their hearing loss, demonstrated effective recoveries following the treatment. Degree of recovery appeared to be related to length of time intervening between onset of deafness and initiation of treatment; *i.e.*, the best recovery was demonstrated by patients who received treatment soon after the occurrence of the

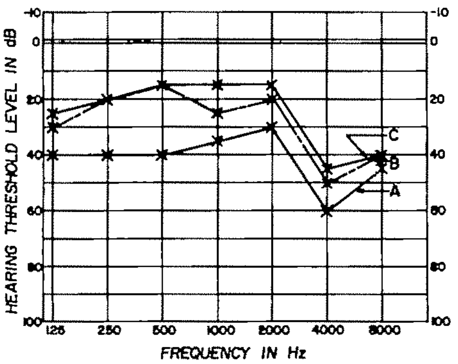

Fig. 3. (Case 1) Left ear audiograms taken: A) before treatment (12-24-74); B) after fourth and final daily treatment (12-28-74); C) one month after final treatment (1-31-75). See Table 2.

deafness while those who delayed treatment showed only partial recovery.

The apparent effectiveness of the treatment did not appear to be related to factors of age, sex, or dosage differences.

Of the ten patients who received the high pressure oxygen treatment after failure to respond to the seven days of contrast medium therapy, four eventually showed a partial recovery of their hearing.

All of the patients were followed for an average of 15 months after treatment with no occurrence of a regression of recovered hearing in that time.

On the basis of these results, it is concluded that the treatment with certain radio-contrast media, sodium salts of triiodobenzoic acid derivatives, represents an effective therapy for "sudden deafness" for cases with less than complete deafness and without accompanying nausea, vomiting, or vertigo. In addition, the distinct difference in response to the contrast medium therapy between patients who had nausea, vomiting, or vertigo and those who did not, suggests that the etiology of sudden deafness in these two groups is different.

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BLOCKING EFFECT OF RADIO-CONTRAST MEDIA ON COCHLEAR DEPRESSION

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SUMMARY — Furosemide injection was used in a total of 72 guinea pigs to induce a cochlear dysfunction similar to the sensorineural loss associated with sudden deafness. Prior to the furosemide administration, 38 of the animals were treated with an injection of one of four radio-contrast media; methylglucamine and sodium diatrizoate, sodium iothalamate, methylglucamine and sodium iodamide, and methlyglucamine diatrizoate. In the control animals, receiving only furosemide, both endocochlear potential (EP) and cochlear microphonic (CM) underwent a severe depression followed by recovery and subsequent secondary depression. Animals pretreated with one of the first three compounds showed little or no EP or CM depression. Animals pretreated with the fourth, methylglucamine diatrizoate, showed the same EP depression as the control animals. The possible mechanism for this blocking effect and its significance in the clinical treatment of sudden deafness is discussed.

Clinically, it is well known that the administration of furosemide as well as ethacrynic acid may induce a sensorineural deafness, particularly in those patients with renal failure. Electrophysiological studies have also demonstrated that these kidney-loop diuretics produce a depression of cochlear microphonics (CM) and endocochlear DC potential (EP) in experimental animals.[1-7] In cases of "sudden deafness" characterized by a similar sensorineural hearing loss, it has recently been shown that treatment with certain radio-contrast media is an effective therapy leading to nearly complete recovery in cases with less than "complete deafness" and without accompanying nausea, vomiting, or vertigo.[8-10] The purpose of this paper is to describe an experimental examination of the effects of contrast medium therapy on "sudden deafness" type sensorineural hearing losses simulated by furosemide depression of EP and CM in guinea pigs. A discussion of possible mechanisms by which contrast medium therapy may improve sudden deafness is also given.

METHODS AND MATERIALS

In all, 72 guinea pigs were used in this experiment. Only animals exhibiting a positive Preyer's reflex were accepted. The animals were anesthetized with 20 mg/kg of pentobarbital sodium intraperitoneally. The head of the guinea pig was tightly fixed in a head holder and a tracheostomy performed. A paralyzing dose of tubocurarine hydrochloride was given intravenously and the respiration of the animal was maintained for the duration of the experimental session by an artificial respirator connected to a cannula in the tracheostomy. The auditory bulla of the animal was opened by a ventral approach and the cochlea exposed. To register the CM, a microdrill was used under a microscope to make two small holes in the bony wall of the basal turn of the cochlea, one over the scala vestibuli and the other over the scala tympani. A pair of steel wire electrodes, 100μ in diameter, tips sharpened to about 10μ and shank glass-coated, were then inserted in the holes and fixed to the auditory bulla. A copper plate indifferent electrode was placed in the animal's mouth.

For the EP, a glass micropipette with a tip pulled to one or two microns and filled with 3 mol potassium chloride was used as the measuring electrode. It was mounted on a micromanipulator and then inserted into the scala media through the round window membrane, scala tympani, basilar membrane, and organ of Corti. An indifferent electrode was inserted in the muscles of the neck.

The CM electrodes were connected to a balanced differential amplifier (Nihonkoden APB-20). Measurements of the amplified CM output in peak-to-peak values were made on a cathode ray oscilloscope. CM amplitudes were registered on a pen-writing oscillograph. The acoustic stimuli for the CM were pure tones of 300 Hz frequency, 500 msec duration, alternating continuously with tones of 3000 Hz, also 500 msec duration. These were produced by two pure tone generators whose outputs were switched alternately by an electronic switch (Rion SBO L A) into the acoustic

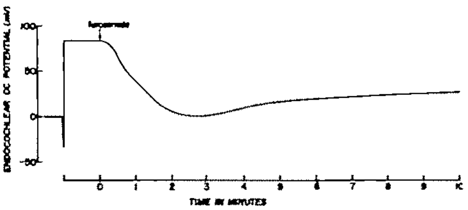

Fig. 1. EP recording from a control animal; effect of injection of 20 mg/kg of furosemide on EP.

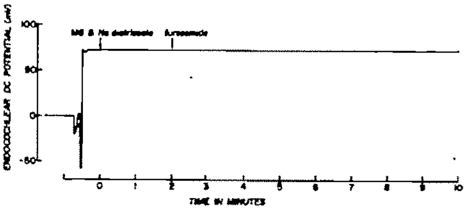

Fig. 2. EP recording from an animal treated with methylglucamine and sodium diatrizoate two minutes prior to furosemide injection; no change in EP.

output system with switching set at a rate of 2/sec. The acoustic stimulus was delivered via a vinyl tube to the external meatus of the animal. Stimulus levels were adjusted empirically for each animal to produce 300μV CM for 300 Hz and 150 to 200μV for 3000 Hz and then held constant during each experimental session. The EP measurements were made by connecting the scala media measuring electrode to an electrometer amplifier (Nihonkoden ADH-2) whose output was recorded on the pen-writing oscillograph.

As an experimental control, the effects of furosemide were first determined by recording EP in 20 animals and CM in another 14 animals after injection of a standard 20 mg/kg dose of furosemide I.V. The effect of four of the contrast media in counteracting the furosemide was then determined in five additional series of animals as follows: 1) in 13 guinea pigs, EP recording, a 456 mg/kg dose of methylglucamine and sodium diatrizoate (76% - Urografin®) was administered I.V. followed after two minutes by the standard 20 mg/kg dose of furosemide, also I.V.; 2) in 11 guinea pigs, EP recording, 480 mg/kg of sodium iothalamate (80% Conray-400®*) given I.V., followed two minutes later by the standard dose of furosemide I.V.; 3) in 6 guinea pigs, EP recording, 480 mg/kg of methylglucamine and sodium iodamide (80% Conraxin-H®) I.V., again followed after a two minute delay by the standard dose of furosemide I.V.; 4) in 3 guinea pigs, EP recording, 390 mg/kg of methylglucamine diatrizoate (65% Angiografin®) I.V. two minutes preceding the furosemide standard dose I.V.; and 5) using CM recording in 5 animals, methylglucamine and sodium diatrizoate at 456 mg/kg administered I.V. two hours before the standard dose of furosemide I.V.

RESULTS

With all 34 control animals who were given only the standard dose of furosemide, a depression of the EP (20 animals) and the CM (14 animals) was consistently observed. The time courses for both potentials, EP and CM were very similar, reaching a minimum value (*i.e.*, maximum depression) at two to three minutes following the injection. This primary depression was followed by a slow recovery over a period of 30 minutes to an hour with subsequent secondary depression extending over several hours. Figure 1 shows a ten minute section, following the furosemide injection, of the EP recording for a representative control animal. Patterns of the CM were similar for both 300 Hz and 3000 Hz.

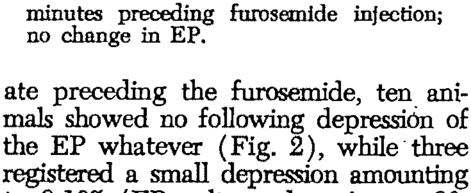

Fig. 3. EP recording from an animal treated with sodium iothalamate two minutes preceding furosemide injection; no change in EP.

Of the 13 guinea pigs given a dose of methylglucamine and sodium diatrizoate preceding the furosemide, ten animals showed no following depression of the EP whatever (Fig. 2), while three registered a small depression amounting to 8-10% (EP voltage dropping to 90-92%) of the initial EP; for these three, the depression occurred within one minute following the furosemide with recovery completed within nine minutes. Of the 11 animals given a preceding dose of sodium iothalamate, seven showed no depression of the EP following the furosemide (Fig. 3); three demonstrated a mild primary depres-

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*Mallinckrodt, Inc., St. Louis, MO.

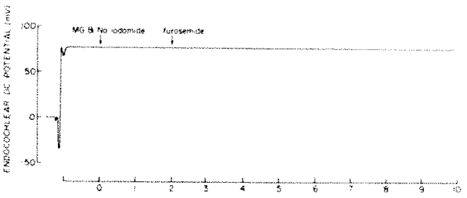

Fig. 4. EP recording from an animal treated with methylglucamine and sodium iodamide two minutes before furosemide injection; no change in EP.

sion, complete recovery and subsequent mild secondary depression of the EP; one registered a decrease in the EP to 40% of the initial value within four minutes but recovered completely by the sixth minute after the furosemide injection. In the group of six guinea pigs treated with methylglucamine and sodium iodamide prior to furosemide administration, no depression of the EP occurred (Fig. 4). In the three animals given a pretreatment dose of methylglucamine diatrizoate, all showed a severe depression of EP following the furosemide, very much the same as seen in the control animals (Fig. 1). It was not possible to see the effects of sodium iodamide alone because this chemical is unavailable unmixed with methylglucamine. In the five guinea pigs prepared for CM recording and treated with methylglucamine and sodium diatrizoate two hours prior to furosemide injection, no CM depression was observed for four animals (Fig. 5), while one animal showed a mild depression of 20μV to 280μV, which then recovered to the initial 300μV level within five minutes (Fig. 6) for the 300 Hz stimulus. Similar patterns were observed for 3000 Hz.

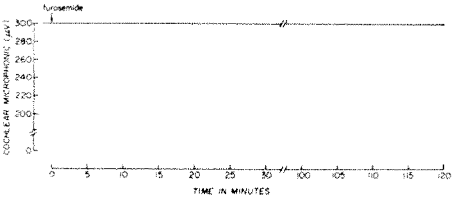

Fig. 5. CM recording, 300 Hz stimulus, from an animal treated with methylglucamine and sodium diatrizoate two hours before furosemide injection; no change in CM.

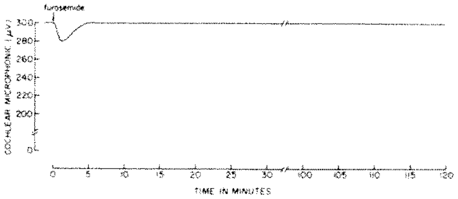

Fig. 6. CM recording, 300 Hz stimulus, from the one guinea pig that showed a mild depression (20μV) of the CM after the furosemide injection; pretreated with methylglucamine and sodium distrizoate two hours before furosemide administration.

In summary, the results indicate that pretreatment with injections of methylglucamine and sodium diatrizoate, sodium iothalamate, or methylglucamine and sodium iodamide, were all effective in blocking the depressing action of furosemide on cochlear function. Only the nonsodium salt material, methylglucamine diatrizoate, was not able to counteract the furosemide induced dysfunction.

DISCUSSION

Cochlear function in experimental animals can be studied by evaluating EP as well as CM. The depression of CM induced by furosemide and ethacrynic acid was first demonstrated by Mathog *et al* in 1970.[1] Date *et al* demonstrated that both diuretics depressed not only the CM but the EP as well.[2] We reported that the initial depression may be followed by a recovery and subsequent secondary depression.[3,4] In order to sustain a normal output of the cochlear microphonic, it is presumed that a normal concentration of electrolytes, particularly Na+ and K+, in the endolymph with a normal endocochlear DC potential is necessary to permit normal function of the outer hair cells. It may be that furosemide depresses the EP by affecting a Na-K-ATPase pump at the stria vascularis. This results in a disturbance of the electrolyte concentrations in the endolymph and, consequently, a depression of the CM. Quick *et al* showed that there is an edema in the intermediate cell layers in the stria vascularis after the injection of 200 mg/kg of furosemide in guinea pigs.[11] Shida *et al* reported that, after injection of furosemide, the K+ concentration in the endolymph was decreased and CM and EP depressed.[12] Therefore, it is conceivable that the sensorineural deafness produced by furosemide is caused by a change from the normal concentration of electrolytes in the endolymph and an accompanying depression of the EP. In view of the foregoing dicussion, it appears that the injection of a sodium salt contrast medium may be effective in preventing furosemide-induced cochlear dysfunction as indicated by the results of this study, by blocking the disturbance of the electrolyte concentrations and depression of EP.

There are various types of cochlear damage that result in deafness. One, represented by streptomycin, kanamycin, or gentamycin induced deafness, is caused by damage to outer hair cells. This type is irreversible and is not curable. Another, such as furosemide or ethacrynic acid induced deafness, is caused by a dysfunction of the stria vascularis. It is usually transient and recovery may occur if the outer hair cells are not severely damaged. With respect to "sudden deafness," some cases appear to recover spontaneously. In a lower percentage of patients, it has apparently been cured by a stellate ganglion block, or by administration of vasodilator agents. Therefore, it has been presumed that sudden deafness is caused by vasospasm or a narrowing of the vessels in the cochlea. It is more reasonable to think that sudden deafness could be caused by dysfunction of the stria vascularis. The histological structure of stria vascularis is reported by Pease[13] to resemble the tubule cells in the kidney and there are other mentions of similarities both histologically and pharmacologically.[14-17] The contrast media in this study are commonly used in pyelography since they are not reabsorbed into the kidney tubules and therefore are excreted in the urine. Their effectiveness in blocking the furosemide-induced cochlear dysfunction as demonstrated in this study may thus involve some type of similar action at the stria vascularis. In view of the effectiveness of a pretreatment with certain of the radio-contrast media, *i.e.,* sodium salts of triiodobenzoic acid derivatives, in blocking cochlear dysfunction induced by furosemide as reported in this study (and the lack of effectiveness of the methylglucamine salt), as well as the observed effectiveness of the contrast medium therapy (using the same sodium salts) in the clinical treatment of sudden deafness reported in a previous paper,[18] it is conceivable that these materials have a specific action in the cochlea that results in restoring normal function to the stria vascularis and a consequent recovery from the hearing loss for a significant number of cases.

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OTOLARYNGIC PATHOLOGY TRAINING PROGRAM

A training program on otolaryngic pathology, presented by the Armed Forces Institute of Pathology (AFIP) in conjunction with the Committee on Otolaryngic Pathology, AAOO, is currently being offered at the Department of Otolaryngic Pathology, AFIP. The course covers both temporal bone pathology as well as surgical pathology of the head and neck area.

Requirements are flexible but preference is given to residents and practitioners in Otolaryngology and Pathology, both military and civilian, who wish to expand their knowledge of ENT pathology. The course, for which there is no charge, is designed to be given quarterly, beginning in January, April, July and October; however, consideration will be given to those seeking shorter training periods.

Requests for course applications should be directed to: The Director, Armed Forces Institute of Pathology, ATTN: AFIP-EDZ, Washington, DC 20306.

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DRUG-RELATED GUSTATORY DISORDERS

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SUMMARY — A review is presented of the drug-induced gustatory disorders that have so far been identified. Metallic, bitter or salty phantogeusias and hypogeusias, often of a dissociated type, which may even develop into ageusia have been described as side effects of treatment with some drugs. Personal observations on six cases are reported in which the gustatory disorders are attributed to the ingestion of phenylbutazone, carbamazepine, chlormezanone and baclofen. After interruption of the treatments these disorders were reversible within weeks to months.

During the last 20 years increasing reports have appeared of gustatory disorders of various types attributed to drug treatment. While such side effects are generally rare, they have been observed with some preparations more frequently and occasionally even in up to one-third of the patients. In Tables 1 and 2 those drugs are listed to which undesirable effects on the sense of taste are attributed. But it is to be expected that both the number of preparations and the frequency of gustatory side effects are in fact greater because the taste disorders are very often not mentioned by the patient or they are not recognized by the doctor as being drug-related.

Several sensory perceptions contribute to the experience of taste. The taste receptors in the oral cavity perceive sweet, salty, sour, bitter and metallic qualities only, but perceive them in finer degrees and variations. The multitude of aromatic components are perceived through the olfactory sensory cells. Yet other sensory perception from the oral mucosa and expectations aroused through the eye also influence the impression of taste. If only one of these four components is missing, the experience of taste is impaired. In what follows, only disturbances of the taste receptors in the oral cavity are discussed.

A reduction of sensitivity for all four taste qualities, sweet, salty, sour and bitter, is termed hypogeusia. Ageusia occurs as soon as these four taste components can no longer be perceived at all. If only one of these qualities is disturbed while taste perception is normal in the other ways, then the condition is one of dissociated hypogeusia or ageusia. Parageusias occur if the taste qualities become confused, sweet stuffs being perceived as salty, for example. A spontaneous uninterrupted, usually metallic taste in the oral cavity is termed phantogeusia.

Frequently metallic phantogeusias, which may sometimes also occur for the bitter and salty sensations, are seen as a side effect of drug therapy. More serious, however, are hypogeusias, often of a dissociated character. The perception of sweetness appears to be affected remarkably frequently. Very often it is the first and in relation to other qualities the most extensively reduced. Moreover, it needs the longest time to recover after interrupting the administration of the drug. Dissociated and general hypogeusias may progress to ageusia if administration of the drug is continued. The development of these symptoms is described both as very slow and, occasionally, as extremely rapid.

In recent years we have seen six cases in which gustatory disorders of differing intensity occurred during the oral ingestion of various medications (Table 3). Neither the primary disease nor other exogenous factors could be regarded as responsible for these gusta-

TABLE 1. MEDICATIONS CAUSING HYPOGEUSIA AND AGEUSIA OCCASIONALLY ASSOCIATED WITH PHANTOGEUSIA OF METALLIC OR BITTER TASTES*

Medication (USAN)	*Trade Names*	*Dosage*	*Illness Treated*
Penicillamine	Cuprimine®	250 mg cap	Rheumatoid arthritis
Levodopa	Larodopa®	250/500 mg cap	Parkinson's disease
Oxyfedrin (INN)	Ildamen®	8 mg tab	Coronary insufficiency
Methimazole	Tapazole®	5/10 mg tab	Hyperthyroidism
Carbimazole	Neo-Thyreostat**	10 mg tab	Hyperthyroidism
Thiouracil	Propacil®	50 mg tab	Hyperthyroidism
Phenylbutazone	Butazolidin®	100 mg tab	Rheumatoid diseases
Amphotericin B	Fungizone®	50 mg vial	Mycotic diseases
Griseofulvin	Fulvicin U/F®	125 mg tab	Mycotic diseases
Azathioprine	Imuran®	50 mg tab	Autoimmune diseases
Salazosulfapyridin	Azulfidine®	500 mg tab	Colitis ulcerosa
Sod. Laurysulphate	(Detergent and foaming agent in tooth pastes)		Care of teeth
Chlormezanone	Trancopal®	100 mg tab	Muscular tension
Carbamazepine	Tegretol®	200 mg tab	Trigeminal neuralgia
Baclofen	Lioresal®**	5/10/25 mg tab	Muscular spasticity

*Frequency of patients with gustatory disorders: Penicillamine - 25 (30%); Levodopa - 4.5 (22%); Oxyfedrin - (0.5%). The remaining drugs were cited less than ten times in the literature.

**Drugs unavailable in the United States.

USAN - United States adopted names; INN - International nonproprietory names.

tory deficiencies. As they regressed in chronological association with stopping of the drug, pharmacological and toxicological influences on the sense of taste were assumed. This view was supported by similar observations by other authors.

Taste was tested with three different concentrations of glucose, salt, citric acid and quinine solutions: 4%, 10% and 40% glucose, 2.5%, 7.5% and 15% sodium chloride, 1.0%, 5.0% and 10.0% citric acid and 0.075% and 1.0% quinine solutions were used. These test solutions were painted on the tongue individually in increasing concentration with a twist of cotton wool. The mouth was washed out between each application of the different qualities. Separate tests of the different areas of innervation of the oral cavity were unnecessary because in drug-induced disorders of taste a generalized lesion is involved. More finely graded test solutions were unnecessary since in any case the patients only visited the doctor for very marked gustatory disturbances. Electrogustometric tests of the anterior tongue were also used as controls.[1]

With these methods ageusia for all four qualities was only found twice. In the remaining four patients there were merely different dissociated disorders (Table 3). The taste for sweet and salty was always affected, but that for acid and bitter only occasionally. The results of the electrogustometric test corresponded to the taste ability for the acid quality. Consequently this test procedure only gave clearly pathological values in four patients. In spite of very severe gustatory disorders for individual qualities, the values of the electrical threshold remained in the normal range for the two cases with normal sensitivity for acid.

In some cases these taste disorders were established after only one to two weeks medication and had reached a considerable degree within two days. If the treatment was continued unchanged, then in some circumstances

TABLE 2. DRUGS CAUSING SPONTANEOUS METALLIC OR BITTER TASTES AND MORE INDETERMINATE TASTE DISORDERS

Medication (USAN)	*Trade Names*	*Dosage*	*Treatment for*	*Frequency of Gustatory Disturbance*	*Side Effect*
Biguanide	Meltrol®	25 mg tab	Diabetes mellitus	3%	Metallic phantogeusia
Ethambutol HCl	Myambutol®	100/400 mg tab	Tuberculosis	"Frequent"	Metallic phantogeusia
Vitamin D	Drisdol®	50.000 u cap	Rickets		Metallic phantogeusia
Gold	Myochrysine®	10-100 mg amps	Rheumatoid diseases		Metallic phantogeusia
Allopurinol	Zyloprim®	100/300 mg tab	Gout		Metallic phantogeusia
Bamifylline-HCl	Trentadil**	150 mg tab	Chronic bronchitis	"Majority of patients"	Bitter phantogeusia
Metronidazole	Flagyl®	250 mg tab	Protozoan infections		Nondifferentiated taste disorder
Lincomycin	Lincocin®	500 mg cap	Bac. infections		Nondifferentiated taste disorder
Acetyl sulfosalicylic acid	Aspirin	500 mg tab	Pains		Nondifferentiated taste disorder
Phenindione	Hedulin®	20/50 mg tab	Thrombosis		Nondifferentiated taste disorder

ageusia developed, as shown by the second case in Table 3. The longer the harmful pharmacological effect persisted, the slower the recovery of the sense of taste after discontinuing intake of the drug. Usually a period of 4 to 6 weeks was required, but in the longest cases it extended over a period of 6 to 9 months.

In three cases the loss of gustatory deficiency was regarded as a side effect of phenylbutazone (Cases 2 to 4). Whereas one of these patients was given a preparation containing only phenylbutazone, the other two were given combined preparations containing either aminopyrine or isopyrine. To what extent these substances were involved in the development of gustatory disorders must remain open. Up to now, spontaneous bitter tastes and hypogeusia or ageusia and persistent dryness of the mouth often lasting for months have only been described for phenylbutazone.[2,3] A reduction of the secretion of saliva, which only occurred in Case 2, cannot, however, explain these taste disorders, so that a direct pharmacological toxic action on the sense of taste was assumed.

Carbamazepine has so far only been suspected three times of having caused

TABLE 3. PATIENTS WITH PHARMACOLOGICALLY INDUCED GUSTATORY DISORDERS

Case	Patient (Age, Sex)	Disease	Trade Names (Daily Dose)	Medication (USAN)	Duration Until Beginning of Symptoms	Sense of Taste				Electrogustometry	Time of Recovery
						Sweet	Salty	Sour	Bitter		
1	37 F	Pain in the back	Muskel-Trancopal comp.® 2 tab 3 t.i.d.	Chlormezanone 100 mg Paracetamol (INN) 450 mg	12 days	A	A	A	A	A	2 wk
2	60 F	Polyarthritis	Elmedal® 1 drag. 2 t.i.d.	Phenylbutazone 150 mg	12 wk	A	A	A	A	A	9 mo
3	36 M	Pain in the back	Tomanol® 1 drag. 3 t.i.d.	Phenylbutazone 100 mg Isopyrin 200 mg	10 days	H	H	H	N	N	4-6 wk
4	35 M	Pain in the back	Demoplas comp® 1 drag. 3 t.i.d.	Phenylbutazone 100 mg Aminopyrine 150 mg	8 days	H	H	N	N	N	4-6 wk
5	47 F	Trigeminal neuralgia	Tegretol® 1 drag. 4 t.i.d.	Carbamazepine 200 mg	2 wk	A	A	N	A	N	6 wk
6	32 F	Multiple sclerosis	Lioresal® 1 drag. 3 t.i.d. Encephabol® 1 drag. 3 t.i.d.	Baclofen** 10 mg Pyritinol** (INN) 100 mg	6 wk	A	A	H	H	H	4 wk

N - Normal; H - Hypogeusia; A - Ageusia.

gustatory disorders of the nature of a bitter phantogeusia.[4-6] The symptoms in the patient observed here (Case 5) consisted of dissociated hypogeusia to ageusia. This may perhaps be explained by the fact that after the onset of the taste disorder the drug was continued for a further six weeks.

The prominent impairment of sensitivity to sweetness and the rapid regression after withdrawing the medication make it likely that in our Case 6 this gustatory disorder was a side effect of the drug. It is true that multiple sclerosis alone can cause gustatory deficiencies. These occur in milder cases exclusively as unilateral gustatory disorders and have only been described as generalized hypogeusia or ageusia in severe exacerbations.[7] Taking into account the report by Cartlidge *et al*[8] it can be assumed that baclofen precipitated these gustatory disorders. Such side effects have so far not been reported for the pyritinol which was administered simultaneously.

Chlormezanone is, like baclofen, a drug with myotonolytic action. It is the main constituent of Muskel-Trancopal comp®. Up to now, only occasional gastrointestinal complaint and dryness of the mouth have been observed. There have been no reports at all of taste disorders. The rapid appearance of ageusia with only a light reduction in salivary secretion and the prompt regression of the symptoms after withdrawing the drug, make it probable that in this case too there is a drug-induced impairment of the sense of taste (Case 1).

Views on the localization of the damage diverge greatly. The most likely explanation is an impairment of the receptor function at the surface, but possibly also in the sensory cell. It appears to have been established for oxyfedrin and acetylsalicylic acid, that only the action on the surface of the tongue can induce gustatory disorders.[9-11] However, an effect on impulse transmission through the taste nerves, or in the ganglion cells and a change in the processing of the stimuli in subcortical centers are considered possible.

Similarly, all attempts to explain the nature of the pharmacologically induced gustatory disorders have so far hardly progressed beyond the stage of speculation. If the drugs that have hitherto been suspected of having gustatory side effects are considered, there are no similarities either in their structures or in their actions. Only baclofen and chlormezanone are both myotonolytics. Certain modes of action have, however, been proposed for individual drugs. Thus the changes in taste during D-penicillamine medication is said to be caused by a reduction in heavy metal ions, in particular of copper and zinc.[12-14] According to recent reports doubts have arisen in this connection and the number of those who deny a relationship in man between copper and zinc and D-penicillamine-induced gustatory disorders is growing. The gustatory side effects of methimazole were explained by the SH-groups in this compound. For acetylsalicylic acid it has been suggested, following experiments in rats, that various adenosine triphosphate-dependent reactions at the receptor surface are inhibited.[10] In this connection it may be of interest that the isolated reduction in sensitivity to sweetness induced by the local action of gymnemic acid is also attributed to inhibition of adenosine triphosphatase.[19]

There is no doubt that there is a certain dose-dependence of pharmacologically-induced gustatory disorders, as is shown by gold and D-penicillamine treatments. Individual sensitivity, however, also seems to be of quite considerable importance. The prognosis is excellent if the toxic drug is withdrawn early. Complete recovery of the sense of taste can be expected. Treatment with vitamin preparations or zinc sulphate[20] therefore appears only to be necessary in exceptional cases.

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AMERICAN RHINOLOGIC SOCIETY

The American Rhinologic Society announces the creation of the Dr. Maurice H. Cottle Award for original clinical and laboratory research in rhinology. The prize will be given to an individual or group of persons for meritorious accomplishment in rhinologic research. The award includes a $500 cash prize from the American Rhinologic Society. Both an abstract (100-2000 words) and the completed paper with illustrations and references in triplicate should be sent to Dr. Pat A. Barelli, Secretary, American Rhinologic Society, Penn Park Medical Center, 2929 Baltimore, Suite 105, Kansas City, Missouri 64108, on or before April 1, 1978. Manuscripts should not contain any indication of the author's identity or affiliation. All of this information should be included in a covering letter. Winners will be notified by May 1, 1978.

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THERMAL INJURY FROM MASTOID BONE BURRS

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SUMMARY — Marked bone temperature elevations and surface osteocyte necrosis result from cutting and diamond burrs used without continuous irrigation. Temperatures generated may injure the facial nerve even if drilling is carried on a millimeter or more distant from the nerve. Irrigation of the operative field maintains bone and nerve temperatures at safe levels. Cutting and diamond burrs obey different thermodynamic principles. Higher rotation speeds, greater applied pressures and greater surface contact area increase cutting burr thermogenesis. Burrs with more flutes generate greater heat than those with fewer flutes. Diamond burr heat generation varies in proportion to applied pressure, but is independent of rotation speed or contact area. Haversian canal blood vessels do not contribute to postoperative revascularization. Rather, vessels immigrate from adjacent intact periosteum, penetrating arterioles and exposed marrow. Surface thermal injury does not impede revascularization and should not impair the healing of tissue grafts applied to the bone surface.

Although several otologists have stated that mastoid cutting and diamond burrs produce thermal injury, none have studied the problem experimentally. This report measures the magnitude of thermal change which mastoid burrs may cause, indicates that thermogenesis varies according to burr design, size, applied pressure and rotation speed, and confirms the need for continuous irrigation to prevent thermal injury to bone and nerve tissue.

REVIEW OF LITERATURE

Orthopedic and oral surgeons, suspecting that thermal injury was interfering with the retention of bone screws and pins, measured the thermal effects of inserting drills and pins into bone. Drilling a pin into a tibial cortex caused local coagulation and subsequent sequestration, which was termed "aseptic thermal necrosis."[1] Experiments with bone drills reported temperatures as high as 140 C .5 mm from the drill hole,[2] 60 C 2 mm distant,[3] and 65.5 C 2½ mm from the hole.[4] Lesser applied forces and dull drills enhanced the temperature rise. Irrigation with Ringer's solution lowered surface temperatures to less than 50 C.[2] High speed drills caused more bone damage than low speed drills unless cooling solutions were used; however, the rate of bone repair was the same, regardless of drill speed and the use of irrigation.

Study of individual bone components revealed that osteocytes exposed to 55 C for one minute, died.[8] Fibroblasts sometimes survived temperatures of 60 C for ten minutes.[9] Temperatures of 50-56 C permanently damaged bone collagen and inactivated tissue enzymes.[10-12] Heat injury produced osteocyte loss and sometimes basophilia of the bone surfaces and mechanical trauma caused basophilic staining of roughened or lacerated bone but no osteocyte necrosis.

Bone repair after thermal injury lacks osteoclastic activity: the surfaces do not resorb.[13,14]* Capillaries invade from intact marginal periosteum and exposed medullary cavities. None arise from transsected Haversian canals. Trabecular bone appears within, and emigrates from any exposed marrow vascular spaces, whether or not the cortex appears devitalized.[15,16] Defects produced by diamond burrs at high or low speeds healed much more slowly than those produced by cutting burrs.[7] Repair proceeded at the same rate whether high or low speeds were used with or without continuous irrigation.[16]

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*Agren E: Personal communication, 1974.

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Dentists reported thermal injury to teeth from dental burrs. Low speed burrs (2,000 rpm) employed without coolant raised tooth surface temperatures as much as 200 C[17] and temperatures 1 mm from the surface at least 75 C,[18] but water irrigation restricted the rise to no more than 8 C[17] to 11 C.[18] Thermogenesis varied proportionally with increases in rotation speed, area of burr contact, and cutting time.[19] Doubling the applied pressure approximately doubled the temperature elevation.[17,18]

Heat damages nerve tissue by inactivating enzyme systems.[20] Mammalian peripheral nerve function is permanently impaired by temperatures of 41 C to 45 C and destroyed by temperatures above 45 C.[21,22] Temperature elevations of as little as 5 C injure mammalian brain tissue.[23] Immersion of peripheral nerves in Ringer's solution causes nerve edema (nerve diameter increased 30% to 52%) if the epineurium has been slit, but no edema if the epineurium is intact.[24]

Study of the thermodynamics of metal cutting and abrasion tools yields helpful insights into the relative performance of cutting and diamond mastoid burrs. The influence of speed variations upon heat generation from cutting burrs is complex. The fraction of the heat generated which flows into the workpiece (in this instance, bone) decreases with increased cutting speed. However, the number of cutting strokes, each contributing heat, increases in proportion to cutting speed. The net result will be a less than linear increase in temperature rise as the cutting speed increases.[25]

A dull cutting tool develops a flat surface on the face which contacts the workpiece. To maintain the cutting efficacy of a dull tool, one must apply greater force against the workpiece. Such force generates greater heat, which flows with greater ease into the workpiece across the flat contact surface. Roughness of the cutting edge also contributes to dullness by encouraging a buildup of bone chips on the cutting edge. This buildup dissipates if the surface is lubricated by a coolant, or if cutting speed is high.

The degree of chip curl also effects heat transfer into the workpiece.[26] The maximum temperature on the tool face lies closer to the cutting edge when the chip is tightly curled. Hence, more heat flows from the tool into the workpiece. Less curled chips absorb more heat from the tool face, reducing tool face temperature and allowing less heat to flow into the workpiece. Coolants reduce the fraction of heat flowing into the workpiece and lessen the total temperature rise in the workpiece.[25]

Diamond burrs are abrasive tools. Abrasion arises when a hard, rough surface slides against a softer surface, digs into it, and plows a series of grooves. The wear rate diminishes as sliding continues, due to blunting of abrasive particles and clogging of the particles by debris from the material being abraded.[26] Irrigating fluids flush wear debris from the surface, allowing abrasion to continue. Fluids cool the workface in the same manner as previously described for cutting tools. Abrasive heating is proportional to the force exerted perpendicular to the surface, but is independent of the area of contact and the sliding velocity (Coulomb's third law of friction). Therefore, diamond burrs should not generate more heat at higher speeds unless more force is applied. Nor should a large diamond burr cause more heating than a small one, if applied force remains the same.

EXPERIMENT 1

This experiment measured the extent of bone surface temperature elevation produced by various typical mastoid burrs, using high and low rotation speeds, with and without continuous saline irrigation. The human temporal bone specimens and saline irrigation solution were maintained at room temperature (21-22 C).

A Hall II air drill provided a measured rotation speed of 123,000 rpm. A belt driven Kavo handpiece powered by a Jordan-Day motor yielded 16,500 rpm. We used sufficient hand pressure to remove bone rapidly, confining re-

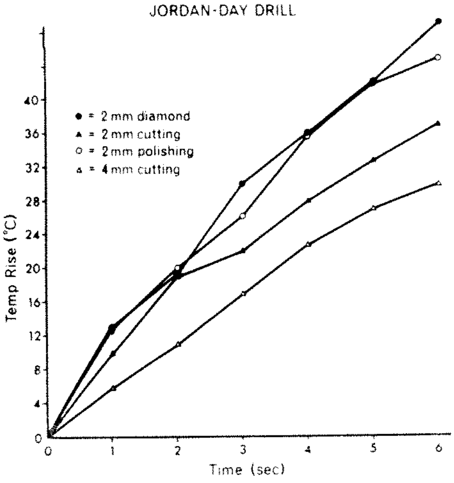

Fig. 1. Temperature rise at bone surface using various dry burrs (average of six trials) at low rotation speeds.

moval to an area 6 mm square for periods of one to six seconds. Immediately afterward we measured the surface temperature by touching it with a thermistor.

The thermistor, which passed through a No. 5 French Baron suction tube, activated a YSI Model 42 S C Telethermometer. The system was calibrated against a laboratory grade mercury thermometer. Deviations from linear response were graphed. The maximum temperature reached in the first second of thermistor application was corrected by interpolation from this graph and recorded.

All burrs were new. The cutting burrs had eight flutes; the polishing burr had 24 flutes. Six trials of each burr and each time interval were averaged. Figure 1 tabulates the surface temperature elevation occurring with various burrs at low speeds (16,500 rpm) without irrigation. A cutting burr of small diameter produced greater surface temperature elevation than a similar burr of larger diameter. Among burrs of the same size, diamond and polishing burrs produced a greater temperature rise than did cutting burrs. The temperature rose in a nearly linear fashion as the duration of burr application increased.

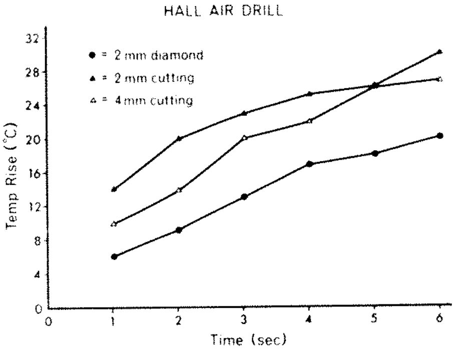

Fig. 2. Temperature rise at bone surface using various dry burrs (average of six trials) at high rotation speeds.

Figure 2 compares the degree of bone heating produced by diamond and cutting burrs of identical diameter at high rotation speeds (123,000 rpm) without irrigation. The diamond burr evoked less surface heating that the cutting burr. (This contrasts with the comparison between diamond and cutting burrs at low speeds.) Once again larger cutting burrs produced less surface temperature rise than smaller cutting burrs. Overall, the surface temperature rise was substantially less at high than at low rotation speeds. The same experiment was repeated with continuous saline irrigation. Burr application and irrigation ceased at the same instant. The temperature rise never exceeded 2 C.

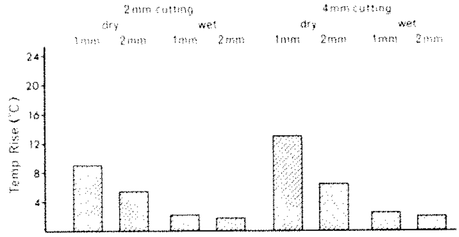

Fig. 3. Difference in heat generation according to burr size and use of irrigation at low rotation speeds.

We then measured bone temperature elevation at 1 and 2 mm depths from the cut surface. The thermistor was inserted into a small drill hole in the bone cortex and sealed in place with nail polish. We attempted to cut to 1 mm

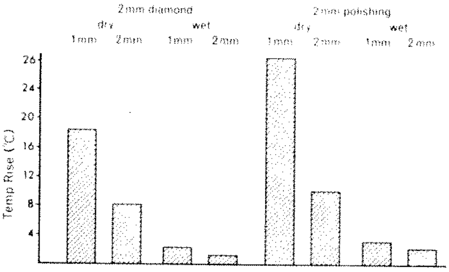

Fig. 4. Differences in heat generation according to burr size and use of irrigation at low rotation speeds.

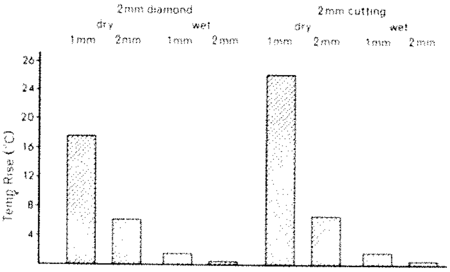

Fig. 5. Differences in heat generation according to burr size and use of irrigation at high rotation speeds.

and 2 mm of the thermistor itself. Six trials were made with each burr, with and without irrigation. Figures 3 and 4 show the results at low rotation speed. The temperature rise 1 mm and 2 mm from the cut surface was less than at the surface. However, the temperature rise was greater for large cutting burrs than small. Diamond and polishing burrs produced substantially more heat than cutting burrs. The temperature elevation varied from a minimum of 9.2 C with a 2 mm cutting burr to a maximum of 24.3 C with a 2 mm polishing burr. The temperature elevation was much less in every trial when saline irrigation was used. In none did the average temperature rise exceed 3.3 C.

Figure 5 shows the results of similar trials using high rotation speeds with and without irrigation. The cutting burr generated more heat than the diamond burr. There was little temperature change (less than 3 C) when continuous irrigation was used. High rotation speeds produced consistently greater bone temperatures 1 mm and 2 mm beneath the surface than did low rotation speeds, but lower surface temperatures than did the same burrs at low speed. Comparison of similar cutting burrs at high and low rotation speeds demonstrated substantially greater bone heating at high speeds. However, diamond burrs differed little in thermogenic capability at high and low speeds.

EXPERIMENT 2

This study evaluated histologic bone injury produced by the same tools and techniques employed in Experiment 1. The dog's mandibular cortex resembles in hardness the cortical plates of the mastoid and the dense bone surrounding the facial nerve canal. Five dogs received intravenous sodium pentobarbital anesthesia. After incising the submental skin in the midline, we elevated the periosteum of the outer mandibular surface to the gum attachment line bilaterally and drilled shallow depressions 1 cm square into the cortices, using the various burrs and rotation speeds, alternately with and without irrigation. Dogs were sacrificed at 30 hours, 1½ days, 3 days, 6 days, 12 days, and 24 days after surgery. The mandibles were removed immediately after death, decalcified, sectioned, and stained with H. & E.

Three parameters of bone injury were studied: 1) basophilic staining of the cut surface, 2) osteocyte loss, and 3) vascularity of the Haversian canal system. Basophilia was judged according to the following criteria: if less than 50% of the cut bone surface showed basophilia, the reaction was termed zero; if more than 50% but less than 100% of the surface was stained, the reaction was 1+; uniform basophilic staining for a depth of 0.0025 mm to 0.2 mm was 2+; instances in which basophilia averaged at least 0.0025 mm thick and in which substantial areas exceeded 0.2 mm were termed 3+. The number of lacunae within 0.25 mm of the cut surface lacking osteocytes was compared with an identical count taken between 0.5 mm and 0.75 mm beneath the cut surface. The ratio of the percent of osteocyte-filled lacunae in the surface 0.25 mm to the percent in the

TABLE 1. BONE INJURY CAUSED BY LOW SPEED BURR (JORDAN-DAY DRILL)

	2mm diamond		2mm cutting		2mm polishing	
	dry	wet	dry	wet	dry	wet
Bone staining	2+	0	1+	1+	2+	0
Havesian canals with functioning blood vessels	59%	69%	57%	64%	46%	57%
Osteocyte damage	2+	0	1+	0	2+	1+

TABLE 2. BONE INJURY CAUSED BY HIGH SPEED BURR (HALL AIR DRILL)

	2 mm diamond		2 mm cutting	
	dry	wet	dry	wet
Bone staining	2+	1+	2+	1+
Havesian canals with functioning blood vessels	68%	73%	58%	68%
Osteocyte damage	2+	0	2+	0

third 0.25 mm was calculated and expressed as a percentage. If this figure was 80% or better, the osteocyte loss was termed zero, 60 to 80% of normal 1+, 40 to 60% of normal 2+, 20 to 40% of normal 3+, and those below 20% 4+. We observed the blood vessel patency of Haversian canals lying within 0.25 mm of the cut surface. The number of Haversian canals containing erythrocytes was expressed as a percentage of the total number of Haversian canals in the 0.25 mm thick surface layer. Percentages were rounded off to the nearest 5%. Tables 1 and 2 tabulate the results of these histologic examinations.

Diamond burrs without irrigation produced thick, diffuse surface basophilia, suggesting considerable thermal damage. Virtually no damage occurred under continuous irrigation. Polishing burrs gave similar results: rather marked surface basophilia with dry technique, but none with wet technique. Cutting burrs produced irregular zones of basophilia with or without irrigation. Mechanical disruption probably caused these changes, particularly since the stained bone exhibited extensive fraying and fragmentation. Irrigation did not ameliorate such damage.

Wet technique yielded a higher percentage of blood-containing Haversian canals than dry technique. The difference, however, was small, and is probably insignificant. In all trials dry techniques caused substantially greater osteocyte loss than wet technique, the difference being most marked with diamond and polishing burrs, but still quite evident with cutting burrs. All cutting burrs, even with irrigation, destroyed some osteocytes.

Diamond burrs at high rotation speeds caused substantially more bone staining than at low speeds, whether or not irrigation was used. Cutting burrs with irrigation produced the same degree of staining at high and low speeds, but without irrigation, high speeds increased the basophilia. Uniform basophilic staining correlated well with greater degrees of osteocyte loss. Dry technique with diamond burrs produced greater osteocyte loss that wet technique, but burr speed variation did not affect osteocyte loss significantly. The depth of the basophilic layer did not lessen over the 24-day, postoperative interval, nor did the surface osteocyte population. The percentage of Haversian canals containing functioning vessels decreased slightly toward the end of the period.

The cut bone surface revascularized poorly. Infrequently a blood vessel penetrated onto the surface, but such vessels arose only from the largest vascular channels of the subjacent bone. On the 24th postoperative day fibroblasts and capillaries were immigrating from nearby intact periosteum and from the largest subjacent vascular channels. Occasionally, a focus of osteogenesis surrounded such a penetrating vessel. New bone also formed within the marrow at sites nearest the areas of bone removal.

CONCLUSIONS

Other authors indicate that temperatures of 50-55 C (13-18 C above body temperature) may cause bone necrosis and that temperatures of 45 C (8 C above body temperature) irreversibly damage nerve tissue. Cutting, polishing and diamond mastoid burrs produce such elevations, sometimes to a depth of 1 mm or more, if no coolant is used. Continuous saline irrigation holds the temperature rise well within acceptable limits, both at depth and on the surface, thereby eliminating the risk of thermal injury to bone and nerve tissue. Irrigating solutions reduce bone temperatures to safe levels only if the coolant adequately contacts the bone surface. One must allow sufficient time for the coolant to flow over the bone surface between strokes. Whether the irrigating solution itself may injure the facial nerve is uncertain. Apparently, the sheath of a peripheral nerve protects the nerve fibers from damage by saline solutions, but once the perineurium is opened, nerve fibers become vulnerable to saline-induced edema.

Diamond and polishing burrs generate more heat than cutting burrs. Large burrs generate more heat than small ones, but small burrs usually generate higher surface temperatures. Applying the same force to a 2 mm cutting burr as to a 4 mm cutting burr will produce higher surface temperatures, though the relation between applied force and heat generation is not linear. However, the area cut by a 2 mm burr is one-fourth the area cut by a 4 mm burr. Since the area available for heat transfer is one-fourth as large, the total heat transferred to the workpiece is less. Cutting and polishing burrs generate more heat at high speeds than low speeds, but diamond burrs do not. This apparent paradox results from differences in operating principles between cutting and abrasive tools. Cutting tool heat generation increases with the number of cutting strokes, and thus in proportion to rotation speed. Diamond burrs obey the thermodynamic laws of abrasive surfaces, in which heat generation is proportional to pressure exerted but is independent of contact surface area and speed of travel. Therefore, a diamond burr maintains its thermal efficiency at high rotation speeds; a cutting burr does not.

Osteocyte loss and uniform basophilic surface staining are the most consistent histologic indices of thermal bone injury. Greater osteocyte loss closely parallels higher observed surface temperatures. Under continuous irrigation, no osteocytes were lost in the great majority of specimens, regardless of the burr used. Without irrigation, at low speeds diamond and polishing burrs caused greater osteocyte loss than cutting burrs, but at high speeds all burrs produced similar osteocyte damage.

A devitalized bone surface might be expected to interfere with revascularization of applied tissue grafts. These experiments revealed that most transsected Haversian canals lacked functional blood vessels whether there was surface thermal injury or not. Revascularization arose from scattered large penetrating vessels, adjacent periosteum, and islands of exposed marrow, none of which suffered thermal injury. It should matter little as regards graft revascularization whether one uses continuous irrigation during bone preparation. However, devitalized bone lacks defenses against infection.[27] Therefore, one should expect thermally-injured bone surfaces to heal poorly and possibly sequestrate in the presence of infection.

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ENDOBRONCHIAL FOREIGN BODY REMOVAL USING THE BRONCHOFIBERSCOPE

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SUMMARY — In certain situations the flexible fiberoptic bronchoscope can augment rigid bronchoscopy in foreign body removal. A case of a successful fiberoptic removal of an endobronchial foreign body (dental bridge) is presented. A wire basket, inserted through the channel of the bronchofiberscope, was used to capture the object.

Rigid bronchoscopy has been eminently successful in the removal of endobronchial foreign bodies for over half a century,[1,2] but if conventional methods ever failed, the only other alternative until recently was thoracotomy. Flexible fiberoptic bronchoscopy (FFB) is slowly being recognized as an important adjunct in foreign body removal in adults. Its extended range of vision, mobility, and comfort are characteristics that lend themselves to successful retrieval of aspirated materials. Only five reports have appeared in the literature describing fiberoptic recovery of foreign objects in the tracheobronchial tree. In each instance standard forceps were employed.[3-7] Recently, Zavala and Rhodes described the use of a basket,* claw,* and Fogarty balloon catheter** in the fiberoptic retrieval of foreign bodies in anesthetized dogs.[7] Although these special extraction tools worked well experimentally, we know of their clinical application in only one other instance which involved the removal of two aspirated teeth via FFB in a traumatized patient.[8]

CASE REPORT

A 20-year-old man was well until two months prior to hospital admission when he suffered a paroxysm of coughing after losing a dental bridge (two incisors). Following that event he had recurrent episodes of pneumonitis unresponsive to antibiotics. He complained of persistent cough, shortness of breath, intermittent fever and weight loss. No foreign object was visualized on repeated chest roentgenograms.

Physical examination was normal except for occasional expiratory wheezes over the right hemithorax. Fiberoptic bronchoscopy was performed through an 8.5 mm endotracheal tube as described by Zavala.[9] The dental bridge was visualized in the right mainstem bronchus embedded in granulation tissue immediately below the orifice to the right upper lobe. The object could not be grasped with the biopsy forceps,† therefore, a wire basket ensheathed in a small plastic tube (1.6 mm diameter) was utilized. Under endoscopic control, the tip of the plastic tube was advanced just beyond the foreign body. At this point the basket was opened and pulled back so the object became enveloped by the separated wires, then entrapped when the basket was closed (Fig. 1). Because of the object's large size, extubation was carried out just prior to its removal.

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*Medi-Tech Corp., Watertown, MA.

**Fogarty catheters obtained from Midwest Medical Laboratories Inc., St. Louis, MO.

†Olympus FB-1C, Olympus Medical Instrument Div., New Hyde Park, NY.

From the Department of Internal Medicine, Pulmonary Disease Division, University of Iowa College of Medicine, Iowa City, Iowa.

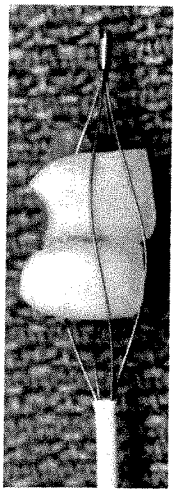

Fig. 1. "Capture" of the dental bridge by the wire basket.

DISCUSSION

The bronchofiberscope has become firmly established as a superb diagnostic and therapeutic instrument in pulmonary medicine.[9,10] The limiting factor in foreign body removal has been the small diameter of the biopsy/aspiration channel which precluded passage of standard bronchoscopy tools. Since the development of small, specialized instruments, foreign body removal via FFB has become practical. Working with a plastic lung and animal models, Zavala and Rhodes[7] found that the basket was most useful in removing bulky objects, and the claw in extracting smaller items with a rough surface. Notably, the biopsy forceps was effective in grasping only a metallic pin. Also, it was demonstrated that an impacted foreign body could be removed by a basket or claw by first passing a Fogarty catheter beyond the object, expanding the balloon, then pulling the catheter to dislodge the object into a larger airway.[7]

It must be stressed that the rigid bronchoscope is the standard instrument for foreign body removal in patients of all ages. Occasionally objects located in inaccessible areas of the lung cannot be reached by this time honored technique. In fact, the problem may be worsened by driving the object into a more peripheral airway. For such a situation, FFB with these new extraction instruments would be ideal. Another instance would be the patient with a mechanical problem, *e.g.*, fractured skull, cervical spine, or mandible, where rigid bronchoscopy is contraindicated.

It has been well-documented that the bronchofiberscope cannot be used in infants and small children because of the small diameter of the trachea and glottis. While it is true that aspiration occurs predominantly in the pediatric age group, there remains a small but significant number of older patients who have this problem. For example, peanuts, gum, paper clips, pins, nails, dental caps and bridges are items prone to be aspirated in the adult population. Anticipation of the type of object to be retrieved would permit optimal rehearsal in a lung model.

In 1921, Jackson made a statement that is fully applicable today: "Endoscopic ability cannot be bought with instruments."[11] Prior training in flexible fiberoptic methods of foreign body removal is absolutely essential.[7] Otherwise, improper technique could lead to any of the following complications: 1) loss of an object in the subglottic area upon withdrawal; elevation of the head during retrieval may prevent this, 2) fracturing an organic object (*e.g.*, a peanut) into small pieces by using the forceps instead of a basket, 3) further impaction of the object in a distal airway, 4) trauma to the tracheobronchial tree, and 5) hypoxemia because of failure to utilize supplemental oxygen.

We realize that the foreign body in our patient could have been removed with the rigid bronchoscope, but we felt confident that our techniques learned in the dog laboratory could be applied to humans, adding to patient comfort and acceptance. Furthermore, we believe that with proper training in foreign body removal, the bronchofiberscope with its extraction instruments will prove to be a useful addition to the armamentarium of the endoscopist.

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HEAD AND NECK CANCER FELLOWSHIP

The American Society for Head and Neck Surgery is pleased to announce that it will sponsor a second fellowship in head and neck cancer at the M. D. Anderson Hospital beginning July 1, 1979. Applications are being accepted now and only until July 1, 1978. The fellowship carries an award of $5,000 in addition to the usual stipend for residents and fellows at the M. D. Anderson Hospital. For further information write: James R. Chandler, MD, Chairman, Fellowship Committee, American Society for Head and Neck Surgery, P. O. Box 520875, Miami, FL 33152.

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AIRWAY MANAGEMENT IN THE PREMATURE INFANT

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SUMMARY — Out of 262 premature newborn patients admitted with a diagnosis of respiratory distress, it was necessary to treat 70 with a ventilator. Of these 70, 25 eventually underwent tracheostomy. Indications for tracheostomy were that of an infant needing prolonged endotracheal intubation greater than one week. The procedure itself was easily performed and an overall complication rate of 7% was the result. Of the patients who underwent tracheostomy, 8% had significant complications. There was no death attributable to the treatment regime. We feel, therefore, that a combination approach starting with the endotracheal tube and progressing to tracheostomy when necessary, provided the best care for premature infants requiring intensive airway management.

In the past, tracheostomy was performed in young children and infants only as a last resort. The explanation for this is the high morbidity and mortality that has been ascribed to the procedure.[1-4] Recently, with more sophisticated equipment and improved techniques, tracheostomy has been performed routinely in neonates and infants with an acceptably low complication rate.[5,6]

In the premature infant, the indications for tracheostomy as compared to endotracheal tube insertion continues to be debated. Those in favor of tracheostomy cite laryngeal trauma by endotracheal tubes as an urgent indication for advising the procedure.[2,5,6] Others evoke the higher morbidity and mortality associated with tracheostomy in this age group supporting more prolonged use of endotracheal intubation.[7,8] Both arguments have merit and we feel that a compromise is possible which better serves the patient.

Earlier experience in newborns has shown that prolonged or repeated endotracheal intubation does cause irreversible laryngeal damage.[9] Also, emergency tracheostomy in an acutely ill neonate can be disastrous. Thus, we evolved a routine in handling these babies with a fairly prolonged initial endotracheal intubation. Then, if it seemed that the premature infant would require ventilatory support for a longer period, an elective tracheostomy was performed. In this manner, we feel that we did only those tracheostomies that were absolutely necessary and minimized complications. Presented here is a summary of our indications, technique, and results over the initial 27 months with a minimum follow-up of nine months.

The patients in this series are all from the Maryland State Intensive Care Neonatal Program at the Baltimore City Hospitals. During the initial 27 months (October 1, 1973-January 1, 1976) there were 938 admissions to the program of which 262 patients were diagnosed as having respiratory distress (excludes cases of congenital heart disease and most surgical diseases). Seventy patients required management with an endotracheal tube and ventilator. Of these, 25 patients underwent tracheostomy after obtaining informed consent from the parents. The vast majority of these patients were diagnosed as having severe respiratory distress syndrome (Table 1). Also, most of the infants who required intensive respiratory care were premature infants of low birth weight (Table 2).

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TABLE 1. DISCHARGE DIAGNOSIS OF PATIENTS TREATED

Diagnosis	*Total No. of Pts. (70)*	*Tracheostomy Pts. (25)*
Respiratory distress syndrome	63	23
Diaphragmatic hernia	2	1
Pneumonia	3	—
Tracheoesophageal fistula	1	—
Hypoplastic lungs	1	1

INDICATIONS

1. *For Endotracheal Tube.* Failure of routine respiratory support including continuous nasal positive airway pressure.

2. *For Tracheostomy.* Prolonged endotracheal intubation (7 days) when further prolonged respiratory support was necessary. Infants requiring frequent reintubation due to displacement of the endotracheal tube or fluctuations in their clinical condition. (A minimum of 20 intubations was necessary.) Infants with such severe disease that the necessity for prolonged respiratory support was obvious from an early stage in their clinical course and in whom even transient extubation might prove lethal.

TABLE 2. WEIGHT AND GESTATIONAL AGE

	Total No. of Pts. (70)	*Tracheostomy Pts. (25)*
Mean birth weight	1.670 gm (810-2410)	947.7 gm (810-2280)
Mean gestational age	31.7 wk (27-38)	30.6 wk (28-34)

TECHNIQUE

TABLE 3. ENDOTRACHEAL AND TRACHEOSTOMY TUBES USED RELATIVE TO BIRTH WEIGHT

T.T. Size	*E.T. Inner Diam. Size (mm)*	*B.W. (gm)*
Shiley "00"	1.5	<1000
Shiley "0"	2.0	1001-1500
Dow-Corning "1"	3.0	>1501

Endotracheal Tube. Initial intubation and subsequent management of these infants was via the oral route. Standard procedures were used for the insertion of the tube under direct vision using the pediatric anesthesia laryngoscope. The diameter of the tube used varied with the infant's size. Generally, a polyvinylchloride tube of inner diameter of 1.5 to 3 mm was used (Table 3). The tube was then securely taped in place and connected to the ventilator. Postintubation x-rays were obtained to identify malposition of the tube or possible traumatic complications. Subsequent management consisted of suctioning a minimum of every four hours, more as necessary. With each suctioning, one-half to one ml of sterile saline was instilled. The tubes were not changed unless occluded. Scrupulous nursing care including close attention, postural drainage, and good sterile technique was followed. Adherence to a rigid routine can avoid many serious complications.

Tracheostomy. Preparation and equipment: Tracheostomy was performed in the Intensive Care Unit without moving the patient from the open radiant heat bed. In other hospitals, however, the Operating Room may be the best place to perform the procedure. A Dow-Corning pediatric Silastic® tracheostomy tube, size 1, was used for infants weighing more than 1,000 gm and a Shiley pediatric tracheostomy tube, size 0, was found to be equivalent (Table 3). For infants weighing less than 1,000 gm, we used the Shiley pediatric tracheostomy tube, size 00.[10]

Before starting the procedure, we made sure that the correct tubes, connectors, and the equipment were all immediately available and absolute sterile technique, both pre- and postoperatively was followed.

Procedure: Infants were placed in

the supine position with the head hyperextended. An endotracheal tube was in place throughout the procedure. After sterile prepping and draping of the surgical field, a solution of 1% lidocaine, either with or without epinephrine, was injected subcutaneously. No significant bleeding was associated with either solution.

Horizontal and vertical skin incisions were used with equal facility. Once through the platysma, which is not a well developed structure in the premature infant, blunt dissection was carried out in the midline until the anterior trachea was reached. Neither the thymus, the thyroid gland, nor the innominate vein complicated the dissection. All were easily retracted out of the surgical field when encountered.

First, the cricoid cartilate was found and then the second and third tracheal rings located. A vertical incision was made in the anterior aspect of the second and third tracheal rings. Occasionally, the fourth tracheal ring was also incised. *A horizontal tracheal incision was never used and no portion of the tracheal cartilage was ever removed.*[10,11]

Next, a nonabsorbable stay suture was placed on each side of the incised trachea in the soft tissue between the tracheal cartilages midway along the incision. The sutures facilitated the initial placement of the tracheostomy tube, the first tube change, and were especially helpful for tube replacement after accidental decannulation. The importance of these tracheal sutures cannot be overemphasized and can be lifesaving.

As the endotracheal tube was then slowly removed, an appropriately-sized tracheostomy tube was inserted. The tracheostomy tube was held in place with tapes which were tied around the neck with the infant's head in a flexed position. Occasionally, an additional 2-0 silk suture was used to secure the tracheostomy tube to the lateral cervical skin. The tracheostomy tubes used in this series, being made with soft plastic, were trimmed for suitable length when necessary.

TABLE 4. AGE AT TIME OF TRACHEOSTOMY AND DECANNULATION IN TEN SURVIVING INFANTS

	Age at Tracheostomy (days)	*Age at Decannulation (days)*
	4.5	31
	5.5	44
	5.5	22
	7	36
	8	36
	9	21
	10	62
	14	24
	14	35
	15	(2 yr)
Average	9	35 (excluding last pt.)

A chest x-ray was taken immediately after the procedure to ensure 1) that the tracheostomy tube and the procedure had not caused a pneumothorax and 2) that the tube was of suitable length, not obstructing either of the mainstem bronchi.

Postoperative tracheostomy care: Forty-eight hours after the initial procedure, the tracheostomy tube was changed. Subsequently, the tube was changed every two to three days or more frequently if there was crusting. Crusting has not been a problem with the tubes used. With the tracheostomy tube *in situ*, the wound was cleansed every four hours, first with peroxide and then Betadine®. Suctioning and postural drainage was performed as with the endotracheal tube.

Decannulation: Decannulation was attempted when mechanical ventilatory support had not been required for a period of seven to ten days and generally took place from two to six weeks posttracheostomy. Prior to removal of the tube, direct laryngoscopy was carried out to exclude glottic and subglottic abnormalities. If the laryngeal examination was normal, the tracheostomy tube was removed 24 hours later (to

TABLE 5. SURVIVING INFANTS ACCORDING TO GESTATIONAL AGE (25 CASES - TRACHEOSTOMY)

Gestational Age (wk)	*Cases*	*Survivors*
28-30	10	1 (10%)
30-35	14	8 (57%)
35-40	1	1 (100%)

TABLE 6. SURVIVING INFANTS ACCORDING TO BIRTH WEIGHT (25 CASES - TRACHEOSTOMY)

Birth Weight (gm)	*Cases*	*Survivors*
1000	3	0 (0%)
1001-1500	15	6 (40%)
1501-2000	5	2 (40%)
2001	2	2 (100%)

allow for subsistence of any acute edema resulting from the laryngeal examination). The orifice was covered with surgical tape and the patient was closely observed. If signs of respiratory obstruction developed, the tracheostomy tube was reinserted. Because of the small tracheostomy tubes used in these infants, gradual weaning using progressively smaller tubes was neither feasible nor necessary.

RESULTS

There were 70 infants who required endotracheal intubation and, of these, 25 patients required tracheostomy. Of the total group, 20 died and 50 survived. Of the group who required tracheostomy, there were ten long-term survivors and 15 who died. In the surviving infants, the age at tracheostomy and decannulation can be seen in Table 4. No patient died as a complication of endotracheal intubation or tracheostomy. All deaths were from the primary disease or its complications. As would be expected, the mortality was highest among those infants of the least birth weight and of the youngest gestational age (Tables 5 and 6). Because the series was not controlled, comparison of survival statistics is not relevant.

The overall complication rate was 7%. Of five patients who had a complication due to our mode of therapy, two had minor bleeding which responded to local measures (Table 7). The other three included one patient with tracheomalacia, one with vocal cord paralysis, and one failure of endotracheal recannulation.

Complications of the endotracheal tube management in this series consisted of one infant who became decannulated and could not be reintubated. This was the only instance in the group where an emergency tracheostomy was performed. The same patient also had a minor episode of bleeding postoperatively from the wound which was easily controlled with local pressure. Four hours postoperatively, the patient died. The immediate postoperative chest x-ray was negative for pneumothorax or other iatrogenic trauma. Postmortem examination showed pulmonary hypoplasia and transglottic edema. In no other patient was iatrogenic, laryngeal or subglottic pathology diagnosed that might have been attributable to endotracheal intubation. Follow-up from 9 to 36 months of age showed no sequelae from the endotracheal tube in the survivors.

Complications due to tracheostomy can be divided into early and late. In our series, the early complications of

TABLE 7. COMPLICATIONS DUE TO AIRWAY MANAGEMENT

	Complications of Tracheostomy Group	*Total Group*
Endotracheal tube management		1%
Tracheostomy		
Minor bleeding	8%	3%
Significant complications	8%	3%
Total	16%	7%

tracheostomy included two cases of minor bleeding from the neck wound. Both responded to local pressure. There were two patients who developed long-term complications: one, tracheomalacia and the other, vocal cord paralysis. In the first patient, decannulation was accomplished without difficulty. Because of symptoms similar to that of croup, his neck was reexplored approximately six months later and mild tracheomalacia was noted. No obstruction to the lumen was found, but a small piece of granulation tissue was removed from the lumen itself. Now, almost three years later, the patient is thriving well.

The second patient who is considered a complication of tracheostomy could not be decannulated. The patient had undergone routine elective tracheostomy, and there was some difficulty in reinserting the tracheostomy tube at a later change for which the patient required a secondary tracheostomy. No significant complication was noted at that time. Later in his hospital course, direct laryngoscopy revealed diminished mobility of both vocal cords. Today the patient is about 18 months old and has been decannulated successfully for the past two months. As to whether this paralysis represents injury to the recurrent laryngeal nerves during the initial procedure or trauma secondary to reintubation is difficult to say.

There were no cases of pneumothorax directly attributable to the procedure. Many of the patients did have spontaneous pneumothorax both before and after tracheostomy and while under endotracheal tube management. This was the result of the disease process itself and the high ventilatory pressures needed to treat it. Of the other possible complications such as hoarseness, aphonia, tracheal necrosis, TE fistula, hemorrhage, accidental decannulation, or obstruction of the tubes, there were none present in our series. There were two patients who died within 24 hours of the procedure. One was the patient cited above who underwent emergency tracheostomy and the second was the smallest baby in our series with an 810 gm birth weight.

DISCUSSION

As severe respiratory distress syndrome is a well-known clinical entity, adding one additional factor such as special airway management permits us to isolate this factor and evaluate it. Thus, we have a group of premature infants in whom the indications, technique, effects, and complications and problems of our management can be isolated. Since there was no attempt at a controlled study, survival data cannot be directly examined.

We feel that initial management by endotracheal tube permits us to do fewer tracheostomies in the borderline premature infants. However, extremely prolonged management with the endotracheal tube past one week can lead to irreversible damage to the larynx and upper trachea. This must be avoided. In our series of 70 patients, one complication was due to endotracheal tube management, and was not a result of prolonged intubation. There were many infants who were easily managed with the endotracheal tube past the magic 48-72 hour mark which some people use as an indication for tracheostomy. It is obvious with our data that initial prolonged management with an endotracheal tube is not only satisfactory, but safe.

After initial endotracheal tube management, once the decision has been made to proceed with the tracheostomy, it must be stressed that this is elective surgery. It is extremely important to have all ancillary equipment and personnel prepared as one would for any elective surgery. The tracheostomy itself is technically quite easy as long as great care is taken not to violate any contiguous structures and the procedure is carried out with an endotracheal tube or bronchoscope in the trachea. Actually, in this age group, most of the dissection after the skin incision may be performed bluntly with a small curved hemostat. We did not try any variations in technique during the series except for vertical versus horizontal skin incisions.

Scrupulous nursing care is extremely important and should never be minimized. Having performed the tracheostomy, care becomes fairly routine. Some of the most important aspects of the care, however, include the necessity for maintaining strict asepsis while suctioning and, secondly, cleansing the tube to avoid crust formations from building up and obstructing the airway. Changing the tracheostomy tube was greatly facilitated by using the traction sutures placed in the trachea at the time of surgery, and these could have been lifesaving if there had been any instance of accidental decannulation.[6,12] Fortunately, we had no such cases, but the feeling of security of having these sutures available until the tract was well formed was very satisfactory. One can easily forget to put these sutures in the trachea at the time of operation, but they are important enough to require special effort in remembering them.

The one problem we feared most was decannulation following tracheostomy.[11,13] As we were dealing with an extremely small trachea, the usual weaning techniques used in older children and adults were not possible. Therefore, we simply removed the tube but did take the precaution of performing a direct laryngoscopy 24 hours in advance. All but one infant converted to the oral and/or nasal breathing without difficulty. We feel that a great deal of our success in easy decannulation was attributable to our using a linear incision in the trachea from the second to the fourth ring with no removal of tissue. In all cases, care was taken to avoid the immediate subglottic area. There was no problem with closure of the tract over the long term.

Much to our pleasant surprise, we found a marked improvement in pulmonary toilet following tracheostomy. Cleansing the airway through the long and relatively narrow endotracheal tube was quite difficult. Lobar atelectasis was quite frequent in the infants with the endotracheal tube. Following the tracheostomy, the pulmonary toilet improved dramatically. Atelectasis and lobar collapse ceased to be a problem. We felt that this was due to more effective suctioning and postural drainage with the wider, shorter airway of the tracheostomy tube. It is our opinion that the improvement in pulmonary toilet some of these infants showed was occasionally critical for survival.

No mortality was attributable to our treatment regime. Overall complications totaled 7% with an 8% incidence of major complications due to tracheostomy.

In no case was there any sign of irreversible, laryngeal, or tracheal damage from the endotracheal tube management. Unquestionably, the endotracheal tube is an important tool in therapy and should be used primarily.

Tracheostomy itself is an operative procedure and does carry an increased risk along with the benefits. Done as an elective procedure and with excellent postoperative care, the risks can be minimized. Also, by deferring tracheostomy until it became obvious that an extremely long period of ventilatory support was going to be necessary, we avoided having to perform the more risky procedure in many patients.

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The Twentieth Annual Meeting of the American Society for Head and Neck Surgery will be held in conjunction with the Society for Head and Neck Surgeons in Toronto, May 28-31, 1978 at the Harbor Castle Hotel. For further information write: Jerome C. Goldstein, MD, Secretary, American Society for Head and Neck Surgery, Division of Otolaryngology, Albany Medical College, Albany, NY 12208.

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IDIOPATHIC MIDFACE LESIONS

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SUMMARY — The term lethal midline granuloma has been used to describe a number of lesions which may present in the midface. A list of possible causes is presented and three entities, midline malignant reticulosis, Wegener's granulomatosis, and malignant lymphoma, are discussed in detail. The pathological descriptions, the clinical features, and the recommended forms of therapy are outlined. It is important to vigorously pursue the patient with a midline facial lesion until a definite tissue diagnosis is obtained. Multiple biopsies may be necessary because necrosis and nonspecific inflammatory changes may be present in various of these disease entities. The correct diagnosis is essential because the treatment of these diseases is different: Wegener's granulomatosis responds best to chemotherapy, whereas midline malignant reticulosis and lymphoma should be treated with radiation therapy if they are localized. Despite conceptual variations, most recent authors believe that these three diseases exist as separate entities, and furthermore, recommend that the term lethal midline granuloma be either dropped from the lexicon or relegated to a descriptive clinical term to be used only until a more definitive diagnosis can be made.

Lethal midline granuloma has been used to describe a large number of lesions which may present in the midface. For many years the precise nature of these processes was often difficult to ascertain (Table 1).[1] As specific diseases or etiologies have been discovered, cases have been relegated to these specific categories until the group now generally includes only Wegener's granulomatosis, malignant lymphoma and a small number of histologically puzzling cases which have recently been considered to be malignant lymphoreticular lesions, designated "midline malignant reticulosis." It is important to make the correct diagnosis because the treatment of these various entities is different. The correct diagnosis is made, not only by clinical symptoms and signs, but more importantly, through histological examination of tissues.

MIDLINE MALIGNANT RETICULOSIS

Pathology. The first of three entities which will be discussed in this paper is midline malignant reticulosis.[2,3] Histologically similar lesions have also been designated as polymorphic reticulosis,[4,5] and nonhealing granuloma of the nose—Stewart's type.[6] Midline malignant reticulosis (MMR) is a malignant neoplasm characterized by an infiltrate of neoplastic cells with an admixture of normal inflammatory cells. The microscopic features were described in detail by Fechner and Lamppin in 1972.[3]

The neoplastic process is notable for its polymorphism (Fig. 1) that is, both small (lymphocytes) and large cells (histiocytes or reticulum cells) are present in contrast to the usual lymphoma in which the population tends to be more uniform. In addition, nonneoplastic inflammatory cells are often present, consisting largely of neutrophils, plasma cells and mature lymphocytes. These may be seen in large numbers near the ulcerated surface of the tumor, or in areas of necrosis deeper in the tissue, but are also found scattered throughout the neoplastic infiltrate unassociated with areas of necrosis.

The nuclei of the tumor cells show a range of size from small to large (Fig.

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TABLE 1. LESIONS WHICH HAVE PRESENTED AS LETHAL MIDLINE GRANULOMA*

Wegener's granulomatosis
Midline malignant reticulosis
Lymphoma of the nose and paranasal sinuses
Syphilis
Tuberculosis
Leprosy
Glanders
Anthrax
Sarcoidosis
Rhinoscleroma
Squamous cell carcinoma
Reparative giant cell granuloma
Eosinophilic granuloma
Osteomyelitis of the facial bones
Factitial ulceration
Histoplasmosis
Blastomycosis
Lupus vulgaris
Adenocarcinoma
Adenoid cystic carcinoma
Basal cell carcinoma

*Modified from Burston.[1]

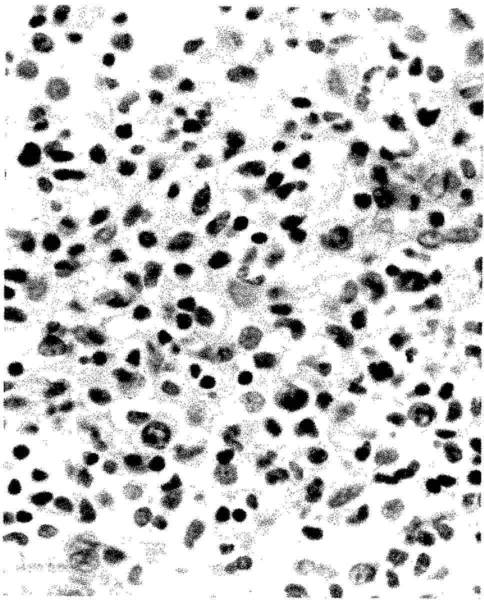
1) and variation in shape, many being irregular, folded or angulated, others round or oval. While the vesiculated nuclei with prominent nucleoli typical of the histiocyte or reticulum cell may be found (Fig. 1), the larger cells often have more uniform, and sometimes hyperchromatic, nuclei. Cytoplasm generally is faintlv eosinophilic or clear (Fig. 1), the latter a feature not so characteristic of the usual histiocytic or lymphocytic lymphoma.

When vasculitis is found, it is characterized by tumor cell infiltration of the vessel wall rather than by inflammatory cell infiltration or fibrinoid necrosis. This feature, coupled with the polymorphism of the infiltrate, may on occasion, particularly in small or superficial biopsies, make the diagnosis of MMR difficult. Rebiopsy may then be indicated in an attempt to obtain an area of tumor less involved with the inflammatory process.

Clinical Features. The clinical features of MMR were classically presented by Stewart in 1933.[7] He described three stages. The first, or prodromal stage, consisted of nasal stuffiness with watery or serosanguinous discharge, without evidence of gross lesions. The second stage commenced with swelling of the external nose and purulent discharge. An ulcer was frequently present within the nose, usually on the inferior turbinate or nasal septum; the ulcer would then spread and lead to perforation of the septum. Ulceration of the hard palate frequently followed. The patient often experienced irregular fluctuations in his temperature and frequently developed abscesses under the cheeks. The blood count would reveal a moderate leukocytosis. The third, or terminal stage, commenced with swelling of the face and sloughing of tissue. Erosion of contiguous structures ensued and the patient often died within one year to 18 months of the beginning of the second stage. There was generally little or no pain with this disease.

Stewart summarized his description by stating that this process was a local indolent ulceration, usually without disseminated lesions, with death resulting from pneumonitis, meningitis, and/or massive hemorrhaging. However, good evidence is present in the literature that this lesion often does disseminate. Spear and Walker[8] reviewed the literature of autopsied cases of lethal midline granuloma in 1956, and accepted six cases and added one of their own. Four of the seven cases manifested disseminated visceral lesions characterized by focal necrosis with pleomorphic cellular infiltrates consisting of plasma cells, lymphocytes, monocytes, and cells described as similar to lymphoblasts and myeloblasts. Glomerulonephritis was not found in any of these cases. Similar intraabdominal dissemination with associated necrosis has been noted at autopsy in some of our patients.

Treatment. There have not been many reports in which the histological aspects of MMR were differentiated from other lesions such as Wegener's granulomatosis, but preliminary reports



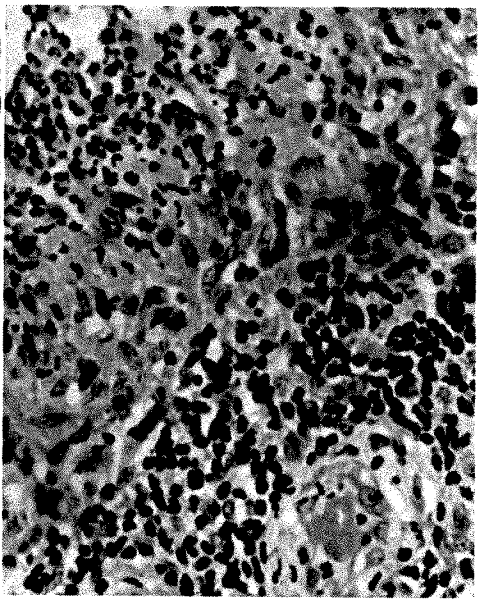


Fig. 1. Midline malignant reticulosis. The polymorphic population of loosely aggregated lymphocytes and histiocytes are characteristic of MMR. Some of the histiocytes contain faintly eosinophilic cytoplasm, while others contain clear cytoplasm; the nuclei tend to be hyperchromatic rather than vesicular. Biopsy of nasal mass (H. & E. X500).

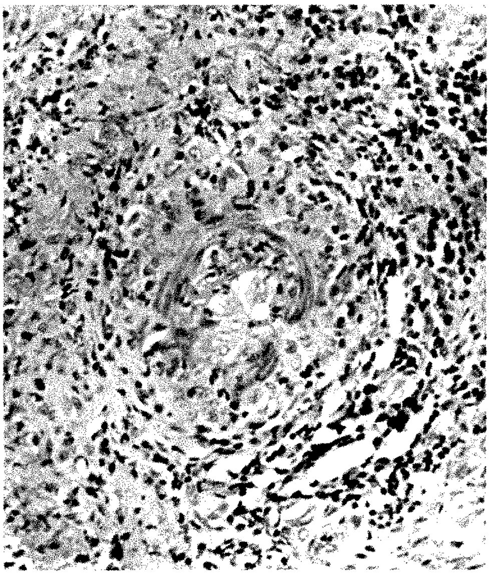
Fig. 2. Wegener's granulomatosis. The margin of a necrotizing granuloma with neutrophils and a surrounding rim of epitheloid histiocytes. Biopsy from nose (H. & E. X300).

indicate that the treatment of choice for MMR is radiation therapy. Eichel *et al*[4] who separated nine cases of polymorphic reticulosis from 33 cases of lymphoma, found a 100% five-year survival in those nine cases treated with radiation therapy. Friedmann,[6] in describing nonhealing granuloma (Stewart's type), reported 15 cases, six of which survived 8 to 15 years after deep x-ray treatment. Ardouin,[9] in the same journal, described two patients with Stewart's type of granuloma, both of whom responded to 1200 rads of radiation therapy.

Fechner and Lamppin[3] reviewed the literature in 1972, and on the basis of photographic documentation came up with 30 acceptable cases of MMR. They found a male to female predominance of five to one, and an age range of 21 to 64 years, with almost half of the patients in the fifth decade. In these 30 cases are included the nine cases of Eichel *et al*, all of whom survived five years or more. Three of the 21 remaining patients are reported by Fechner and Lamppin. These were treated with 4000-6000 rads and were alive and well with no evidence of disease from 8 to 21 months after therapy. Of the other 18 cases accepted by Fechner and Lamppin, 10 had disease beyond the face at autopsy; this group of patients was treated with varying doses of radiation therapy. Disseminated sites of disease at autopsy included trachea, esophagus, liver, kidney, spleen, adrenal, pituitary, ear, lung, lymph nodes, and skin.

WEGENER'S GRANULOMATOSIS

Pathology. The pathological features of Wegener's granulomatosis (WG) are described by Godman and Churg.[10] Three primary features are mentioned. The first is necrotizing granulomatous lesions in the upper air passages or in the lower respiratory tract, or both. These lesions are characterized by a severe granulomatous reaction, giant cells, fibrosis, necrosis, and granulation tissue. Secondly, they described a gen-



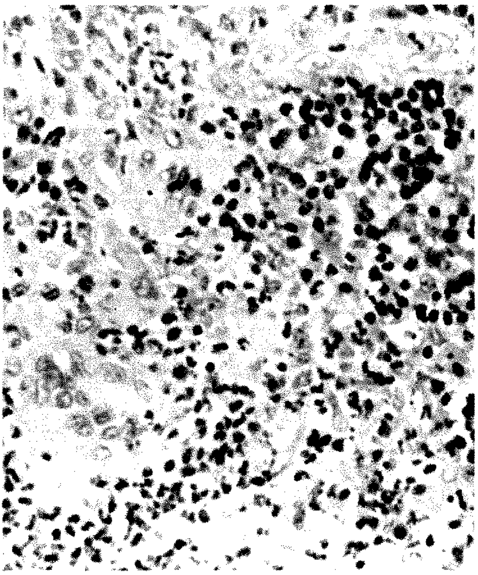


Fig. 3. Wegener's granulomatosis. Necrotizing granulomatous vasculitis with segmental fibrinoid necrosis (H. & E. X250).

Fig. 4. Wegener's granulomatosis. Granulomatous inflammation with epithelioid histiocytes, lymphocytes, plasma cells and giant cell (H. & E. X450).

eralized focal necrotizing vasculitis, involving both arteries and veins, almost always in the lungs, and more widely disseminated in other sites. Microscopic features consist of acute inflammation of the vessel wall, fibrinoid necrosis, thrombosis, and eventual healing by fibrosis. All stages in the progression of the vascular lesion are found at any one time. Thirdly, a focal and segmental glomerulonephritis, characterized by fibrinoid necrosis of capillary loops, capsular adhesions, and evolution as a granulomatous lesion is described. The term focal indicates that some, but not all, glomeruli exhibit lesions; the term segmental indicates involvement of some, but not all, tufts of an individual glomerulus. The renal lesion, as seen under the light microscope, resembles other diseases thought to be of hypersensitivity origin. In two of seven patients studied by electron microscopy, electron dense deposits were found on the epithelial side of the basement membrane.[11] Only a few cases of immunofluorescent staining of glomeruli for immunoglobulin and complement deposition have been described;[12] the usual staining pattern is a coarse granular type consistent with immune complex deposition. In addition, other features seen with high frequency include massive or multiple necroses in the spleen and visceral granulomata.

Biopsies of the nasal lesions generally show extensive necrosis and inflammation, particularly in superficial areas. More than one biopsy may be necessary to demonstrate the typical granulomatous inflammation surrounding foci of necrosis (Fig. 2) and granulomatous vasculitis (Fig. 3). Giant cells may be seen (Fig. 4) in a background of benign appearing histiocytes, neutrophils and lymphocytes.

Clinical Features. In 1958, Walton[13] reviewed the world's literature and found 56 cases of WG which had come to autopsy. In this series, he found a male to female predominance of three to two and an age range of 12 to 75 years with a peak incidence in the fourth and fifth decades.

The disease as described by Walton usually has an insidious onset with nonspecific symptoms of infection in some part of the respiratory tract. Often the constitutional upset is out of proportion

TABLE 2. SYSTEM INVOLVEMENT IN WEGENER'S GRANULOMATOSIS IN 18 PATIENTS*

Respiratory tract	100%
Renal	83%
Joints	56%
Skin or muscle	44%
Eye	39%
Middle ear	39%
Heart or pericardium	28%
Nervous system	22%

*Data from Fauci and Wolff.[12]

to the apparent intensity of the local lesion, and the patient seeks advice because of persistent malaise, fever or weakness. Untreated, the course is usually rapid and fulminating, progressing to death in an average of five months, occasionally in as little as four weeks. A few patients have had a more chronic illness with periods of remission, and survival for up to four years. Spread of the inflammatory process leads to extensive mucosal ulceration and cartilaginous or osseous destruction in the nose and palate on the one hand, and to widespread pulmonary consolidation of the other. Once signs of dissemination have occurred, the general condition has always deteriorated and death ensues from uremia or secondary bronchopneumonia. Untreated, 82% of the patients die within one year.

Recently, the concept of limited WG has appeared, indicating the absence of renal involvement. Lung involvement is present in most of these described cases.[14-16] McDonald *et al*,[17] however, reported upper respiratory involvement alone occurring in 9 of 52 cases. The prognosis in limited WG is probably better, since only 6 of 16 cases in one of these series[15] died of the disease.

A system-by-system review[12] of WG (Table 2), indicates cardinal findings in the respiratory system in both generalized and limited WG; the diagnosis should not be made in the absence of respiratory tract involvement.

Mucosal ulcerations, septal perforations, saddle nose deformities and varying degrees of paranasal sinusitis are common findings in upper respiratory tract involvement; radiographic abnormalities of the sinuses were found in 17 of 18 patients[12] with air fluid levels indicative of secondary bacterial infections commonly seen. The most common pathogen in these episodes of sinusitis was *Staphylococcus aureus.*

Any area of the lung may be involved with WG. The radiographic pattern may consist of solitary or multiple nodular densities or infiltrates, either poorly defined or sharply circumscribed.[18,19] These vary from 1-9 cm; they may be unilateral but are usually bilateral. Cavitation is common with occasional air-fluid levels present.[19] The pulmonary infiltrates may be quite transient, although most patients do have infiltrates at one time or another. Mediastinal lymph node enlargement is very rare. Respiratory symptoms are quite variable; infiltrates are frequently asymptomatic, although a low grade cough, chest discomfort or pleuritic pain is common. A few patients have been reported to have died from massive pulmonary hemorrhage.

The course of the renal disease without therapy consists of proteinuria, hematuria, red cell casts, and rapidly progressing renal failure. Unlike the pulmonary disease in WG which may be fleeting and transient, the renal disease has not been known to spontaneously arrest or regress. Renal biopsies were performed in 16 of 18 patients in one series[12] with normal biopsy results in only three. Interestingly enough, 2 of 16 patients had normal urinary sediment and normal renal function, and yet had unequivocal early glomerulonephritis.

Eye involvement may consist of corneal-scleral ulceration, necrogranulomatous keratitis, granulomatous uveitis, conjunctivitis, orbital pseudotumor, and proptosis. The proptosis is usually due to erosion of the sinuses with disease invading into the orbit.

The ears were involved in 15 of 56 of Walton's patients with otorrhea and/or decreased hearing being the most common finding. A serous effusion was also commonly seen. Linthicum and Schwartzman[20] reported two patients whose initial symptoms of WG were otorrhea and hearing loss and stated that surgical treatment is contraindicated.

Walton[13] reported that 25% of his patients had laryngeal involvement, but in only half of these were there symptoms. Thomas,[21] in a review of the literature, pointed out that there appeared to be a predilection for WG to involve the subglottic area with manifestation of ulcers, granulation tissue and sometimes vocal cord edema. In only three reported cases,[21,22] did WG present originally in the larynx.

Cardiac findings include necrotizing coronary vasculitis and pancarditis, granulomatous inflammation of the epicardium, and focal pericarditis. Death secondary to cardiac causes occurred in 9 of 56 cases.[13]

Joint changes were reported in 22 of Walton's 56 patients and in 10 of Fauci and Wolff's 18 patients. These changes included polyarthralgias and true arthritis. The joint symptoms did not correlate with the total disease activity.

The nervous system may be involved by both granulomata on the meninges and also by vasculitis of the cerebral vessels with resulting cerebrovascular thrombosis, intracranial hemorrhage, or subarachnoid hemorrhage.

The skin may manifest ulceration and necrosis secondary to acute necrotizing angiitis with thrombosis. Hemorrhagic ulcerations have been described on the palms, arms, as well as on the nose.[23]

Laboratory findings include a normocytic normochromic anemia with a hematocrit in the low thirties and a normal or elevated white count without evidence of eosinophilia. Thrombocytopenia and leukopenia are not seen prior to therapy. An elevated erythrocyte sedimentation rate and hyperglobulinemia are present. IgG and IgA are elevated with IgM significantly depressed; however, these findings are not significantly different from those of patients with chronic sinusitis.[24] Rheumatoid factor is elevated in approximately half of the patients and complement is either normal or slightly elevated. The lupus erythmatosis preparation and the antinuclear antibody preparation are usually negative. Delayed hypersensitivity skin reactions are normally present.

Treatment. Many agents have been used in the treatment of WG. Antibiotics are useful in the control of secondary infections, but the underlying disease relentlessly progresses. Although corticosteroids may decrease the inflammatory reaction and improve symptoms early in the disease, they cease to be of any benefit when the disease progresses to significant pulmonary or renal involvement.[12]

Cytotoxic chemotherapy has resulted in the dramatic arrest of the disease activity and also improvement of renal function. Fauci and Wolff[12] described 18 patients, 15 of whom lived long enough to receive chemotherapy. Two died despite what seemed like adequate doses of the chemotherapeutic agent but the other 13 went into complete remission; as of 1973, six of these patients were off all therapy. Israel and Patchefsky[16] described eight patients treated with chlorambucil or azathioprine. Seven of the patients had a good response, although a few were concurrently on prednisone; one patient died secondary to the chemotherapy with no evidence of WG at autopsy. Novak and Pearson[25] described four cases which had previously proved unresponsive to steroid treatment; they treated them with cyclophosphamide, given in massive intravenous doses in one near terminal patient and orally in three others. All had rapid amelioration of all signs and symptoms of their disease. Two of these patients were off all therapy 12 to 20 months after onset of therapy, and the other two were asymptomatic on low dose cyclophosphamide (Cytoxan®). Capizzi and Bertino[26] described two cases who went into remissions of 30 and 26 months duration on methotrexate therapy.

The duration of treatment with chemotherapy is open to question. In patients with prompt and unequivocal remission, Fauci and Wolff[12] recommend tapering and stopping the treatment one year after all traces of disease activity disappear. In the six patients in whom therapy was stopped, it had been given for an average of 30 months. The following cyclophosphamide protocol is suggested[12]: 1-2 mg/kg/day orally; if after 10-14 days a favorable response is not seen, the daily dose is increased by 25 mg and kept there for an additional 10-14 days; the dose is increased every 10-14 days until a definite response is seen, or until leukopenia (white blood count (WBC) less than 3000) supervenes. Patients are then maintained on that dose with frequent monitoring of WBC. Often doses that were well-tolerated initially were later found to be excessive, based on neutropenia. Patients who were already on corticosteroids have had these steroids discontinued by slow taper. The persistence of mild sinus symptoms in patients who had severe sinus symptoms need not necessarily be taken as an indication to increase cytotoxic therapy or renew therapy that has been discontinued. The adverse effects of cyclophosphamide include leukopenia, anemia and thrombocytopenia, mild alopecia, hemorrhagic cystitis, azospermia and ovarian destruction. In patients of child-bearing age, another chemotherapeutic agent such as azathioprine (Imuran®) should be considered to avoid injury to the patient's reproductive organs.

Etiology. The hypersensitivity theory is the most prominent theory of the etiology of WG with advocates stating that since respiratory tract disease usually precedes systemic involvement, the respiratory tract is the initial site of sensitization, with later renal involvement. The striking clinical response to cytotoxic drugs which cause various degrees of immunosuppression is in keeping with the hypersensitivity postulate. However, no unequivocal evidence to support this idea has been found and no offending antigens or noxious stimuli have been isolated. Another theory is that WG is an obscure form of infectious disease. However, no evidence is found in the literature to support this concept, and moreover, extensive bacterial, fungal and viral cultures have been nonrevealing.

NASAL AND PARANASAL SINUS MALIGNANT LYMPHOMA

Pathology. The last disease to be discussed is malignant lymphoma. Eichel *et al*[4] reviewed the Mayo Clinic experience over 30 years with lymphoma of the nose and found 33 cases classified as lymphoma, lymphosarcoma, reticulum cell sarcoma, or Hodgkin's disease with primary manifestation in the nasal cavity. Twenty-four presented as classical lymphomas with findings of dense, sheet-like infiltrates of tumor cells permeating the stroma or replacing atrophic submucosal glands, small vessels, and nerves. The mucosa was ulcerated in 18 tumors and when it was intact, the sheets of tumor cells were usually found just beneath it. Several of these tumors extended into muscle. The cells were usually more densely packed and were more homogeneous than in MMR. The remaining nine cases were separated out because of the polymorphic appearance of the cells, probably representative of MMR.

The histologic classification of neoplasms of lymphoid tissue is continually evolving. It is not the purpose of this paper to discuss the most recent classifications of lymphomas, but rather to alert the clinician to the possibility of lymphoma in the differential diagnosis of midline facial lesions. It should be sufficient to note that, in contrast to MMR, malignant lymphoma is characterized by a relatively uniform, monotonous population of tumor cells (Fig. 5). Most lymphomas in these sites, as in other extranodal locations, are of the histiocytic or reticulum cell variety (Fig. 5), and nodular or follicular lymphomas are rare. The inflammatory element seen in MMR and WG is absent, except at the surface in ulcerated areas.

Clinical Aspects. In the series of Eichel *et al*,[4] the median age and sex ratio were essentially identical between lymphoma and MMR, in the early 50s and two to one male to female, respectively.

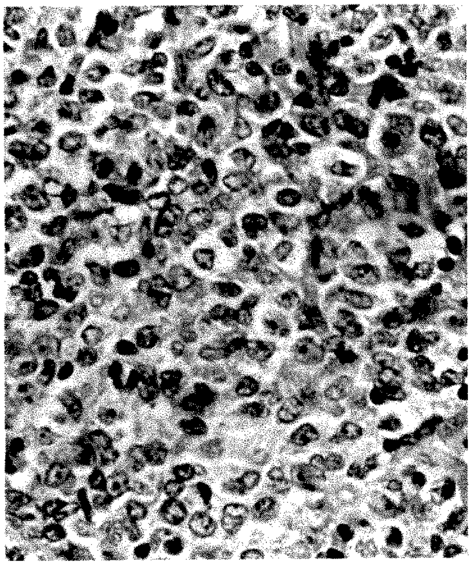


Fig. 5. Malignant lymphoma, histiocytic type. Relatively uniform population of histiocytes with scanty cytoplasm; many of the cells have vesicular nuclei (H. & E. X500).

TABLE 3. COMPARISON OF INTRANASAL FINDINGS IN LYMPHOMA AND MIDLINE MALIGNANT RETICULOSIS*

	Lymphoma (N = 24)	*MMR (N = 9)*
Bilateral	17%	55%
Mass	71%	33%
Ulcerated mass	29%	11%
Ulceration without mass	0%	55%
Fistula or perforation	0%	44%

*Data from Eichel *et al.*[4]

Symptoms were quite similar also, with progressive nasal obstruction present in over half of each group of patients. Symptoms of long standing sinusitis were more commonly present in patients with MMR and these findings were present usually for a longer duration in the MMR patients. Physical findings were fairly similar with the following exceptions (Table 3); lymphoma was present bilaterally in the nose in only 17% of the lymphoma patients and in 55% of the MMR patients. Seventy-one percent of the lymphoma patients and 33% of the MMR patients had a mass. Ulceration without evidence of a mass, or a septal perforation were each present in one-half of the MMR patients. None of the lymphoma patients exhibited either a septal perforation or an ulcer without evidence of a mass lesion. Birt,[27] in describing nine cases of reticulum cell sarcoma of the nose and paranasal sinuses, states that in two-thirds of his cases, the differential diagnosis appeared to be between neoplasm and granuloma. All of his patients had swelling of the soft tissue of the face. In three cases, the lateral nasal wall was displaced medially and in one case the septum was swollen but only one patient presented with friable tissue in the nose.

Nasal obstruction and cheek swelling were the most common initial complaints in a series of 19 patients with paranasal sinus lymphoma.[28] The antrum was the most common primary site; but regardless of site of origin, the disease had usually spread to another sinus or adjacent structure by the time the diagnosis was established. Cervical adenopathy was not present initially and implied a poor prognosis when it developed following adequate radiotherapy to the primary lesion. When recurrences or distant metastases became manifest, they did so within nine months of the initial diagnosis.

Treatment. It is difficult to evaluate the therapy in the series of Eichel *et al* because of the different types of radiation therapy used over the 30-year span of the series. Surgery was also used in about one-third of the patients. Yet, it is significant that there was only a 41% five-year survival in those 18 lymphoma patients whose disease was limited solely to their noses, whereas there was a 100% five-year survival in the cases described as representing polymorphic reticulosis (MMR). In treating lymphomas originating in the oral cavity or paranasal sinuses with radiation therapy, Wang[29] reports a 65% five-year survival (15 of 23 patients) in those patients without evidence of cervical or distant metastases. He suggests a dose of 5000 rads in five weeks and recommends treating the regional lymphatic drainage area only if palpable nodes are present. In general, the treatment of localized lymphoma is radiation therapy, whereas, if the disease is disseminated, chemotherapy is usually the treatment of choice. To determine the extent or stage of the lymphoma, many diagnostic tests have been advocated including chest radiography, liver-spleen scan, bone scan, lymphangiogram, bone marrow biopsy, intravenous pyelogram, radiography of the alimentary tract, and exploratory laparotomy.

SUMMARY

Three distinct diseases have been presented: MMR, WG, and nasal and paranasal sinus lymphoma, all of which may have the same clinical presentation in the midface, and which at one time or another, have all been called lethal midline granuloma. Histologic diagnosis is necessary to correctly identify the specific disease entity, and this may require several biopsies to obtain diagnostic tissue. In this paper, an attempt has been made to clearly separate these three diseases; however, in practice it is not always easy to do so. The waters are muddied by the following circumstances: 1) the biopsy samples may not be adequate; 2) Wegener's granulomatosis, which is usually thought of as a generalized disease, may be limited to the upper respiratory tract; 3) midline malignant reticulosis at times may be disseminated; 4) lymphoma even more frequently is disseminated at initial presentation; 5) prominent pathologists disagree on the classification of these diseases. Friedmann[6,33] considers Wegener's type and Stewart's type of midline granuloma to be variations of the same underlying pathological condition. More recently, most authors believe, as do Fechner and Lamppin,[3] that MMR is a type of lymphoma. It is difficult to sort out these three diseases in the older literature. Kassel *et al*[2] so eloquently state, "the history of lethal midline granuloma, as a disease entity, is a tangled web of scattered case reports, a plethora of synonyms, and until recently, a disturbing lack of morphological documentation."

Despite conceptual variations, most recent authors believe that these three diseases exist as separate entities, and furthermore, recommend that the term lethal midline granuloma be either dropped from the lexicon or relegated to a descriptive term to be used only until a more definitive diagnosis can be made.

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XII WORLD CONGRESS OF OTORHINOLARYNGOLOGY

The XII World Congress of Otorhinolaryngology will be held June 21-26, 1981 in Budapest, Hungary. Preliminary communications, recommendations and suggestions, should be directed to Prof. Dr. L. Surján, President, XII World Congress of ORL, H-1389 Budapest, Pf: 112 Hungary.

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INTERCELLULAR JUNCTIONS IN THE ORGAN OF CORTI

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BOSTON, MASSACHUSETTS

SUMMARY — The intercellular junctions between adjacent supporting cells and between apposed hair and supporting cells in the organ of Corti of cat and human were studied. At the endolymphatic surface, the intercellular space was closed by a series of tight junctions (zonula occludens), whereas there were no tight junctions at the basilar membrane surface of the neuroepithelium. Beneath the adlumenal zonula occludens between adjacent supporting cells, a zonula adherens (intermediate junction, "desmosome") was found. Many gap junctions joined apposed supporting cells both within and below the endolymphatic junctional complex. Below the zonula occludens between apposed hair and supporting cells, membrane specialization sharing the morphological characteristics of both the macula adherens and zonula adherens was found. Between areas of tight junctional specialization in the junctional complex between hair and supporting cells, there were short areas of parallel limiting membranes separated by a 20A intercellular space. These areas were suggestive but not characteristic of gap junctional specialization. The functional significance of the junctional specialization between cells in the organ of Corti was discussed.

Vertebrate epithelial cells are joined by three types of junctions as characterized by their physiologic function and ultrastructural anatomy.[1] Junctions of exclusion (zonula occludens, tight junctions) serve as a permeability barrier to the intercellular passage of molecules.[2,3] Junctions of attachment (desmosome, macula adherens, zonula adherens) are presumed to serve a mechanical role of attachment between apposed cells. The gap junction, previously included among "tight junctions" (fascia occludens), has recently been differentiated from the true occluding tight junction by improved resolution achieved with transmission electron microscopy and *en bloc* uranyl acetate staining[4] and by the freeze-fracture technique.[5] The gap junction, in contrast to the tight junction, allows the passage of small molecules through the intercellular space.[4] In addition, the gap junction is the site of intercytoplasmic passage of small molecules[6] and serves as a site of electric coupling between cells.[7]

The junctions between epithelial cells in the organ of Corti recently have been the subject of extensive study. The presence of tight junctions (zonula occludens) at the endolymphatic surface of cells of the organ of Corti is well established.[8-14] Studies employing the freeze-fracture technique have confirmed the presence of an occluding junction at the reticular lamina.[15,16] The location of tight junctions in the organ of Corti has important implications for its physiology. These junctions affect the composition of inner ear fluids and hence the electrophysiological properties of the receptor neuroepithelium. Gap junctions have been found between adjacent supporting cells in various species[13-15] and between adjacent hair and supporting cells in the basilar papilla of the alligator lizard.[13] The location of gap junctions within the organ of Corti suggests the possibility that adjacent supporting cells, and in some cases adjacent hair cells and supporting cells are electrically coupled.

To compare the junctional complexes found in the auditory neuroepithelium of the alligator lizard with those in the mammal, the organ of Corti of cat and human was examined.

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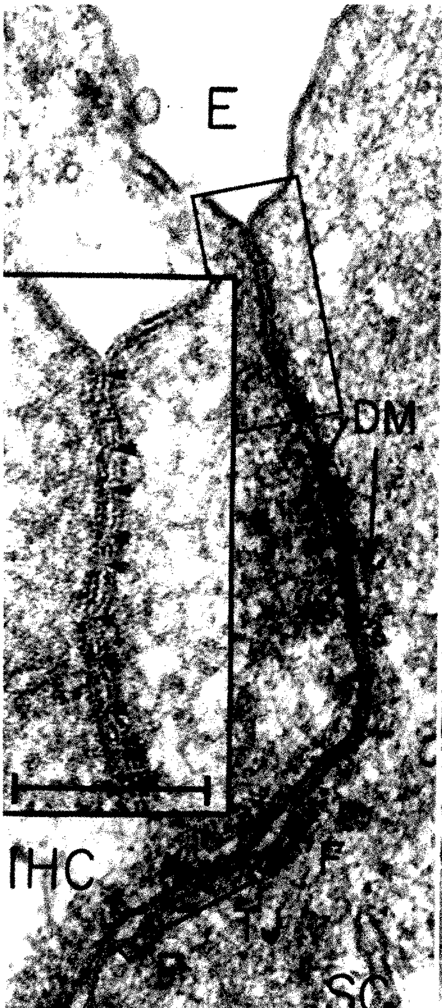


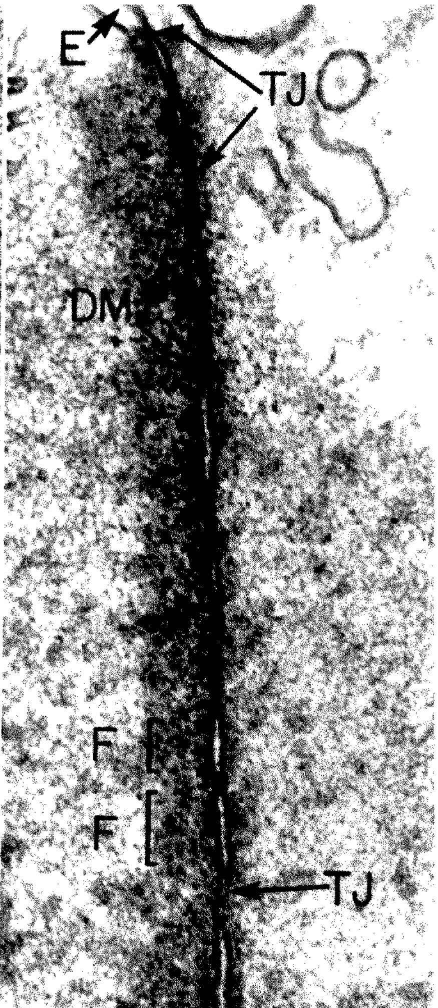
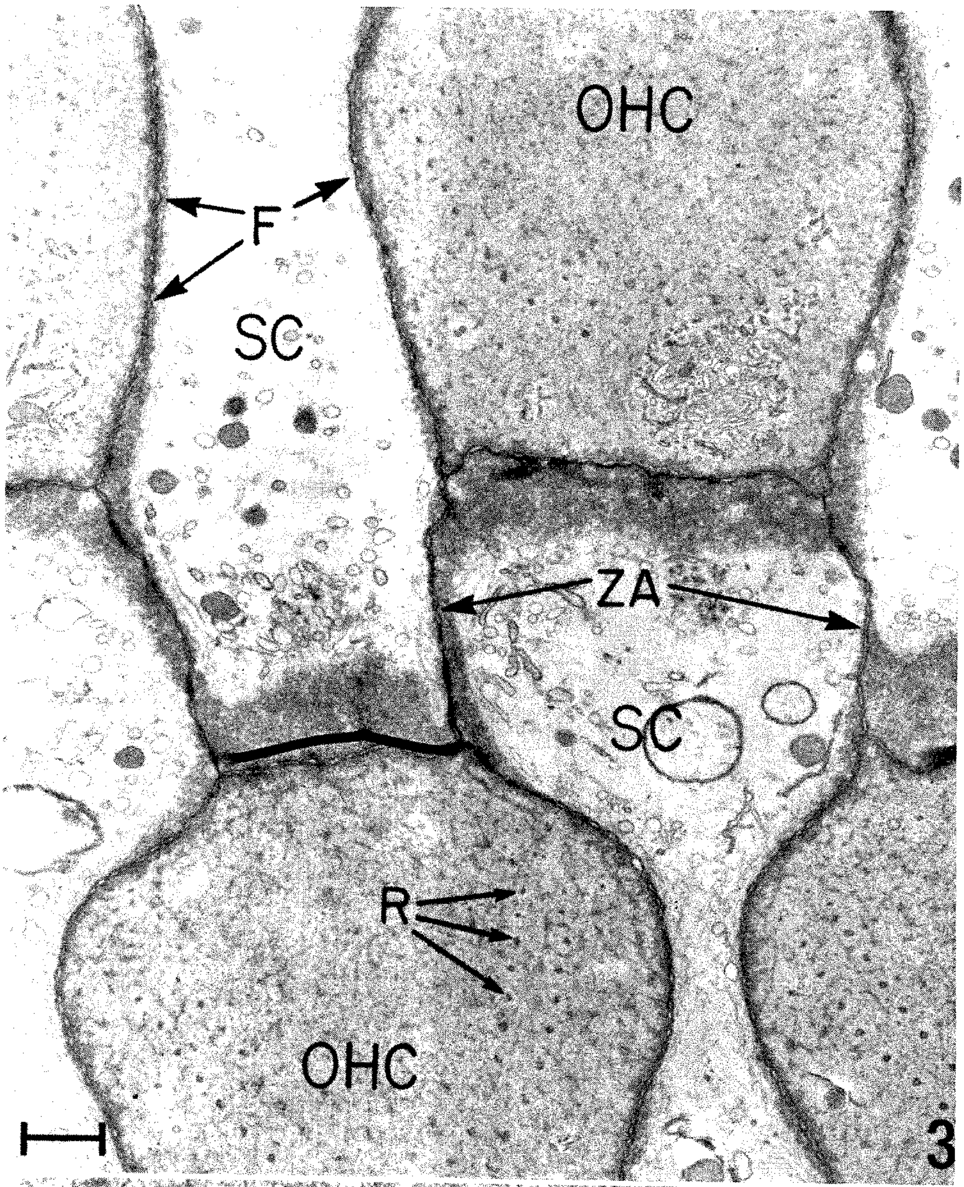


Fig. 1. Endolymphatic junctional complex between apposed inner hair cell (IHC) and supporting cell (SC) of the human. At the endolymphatic surface (E), the outer leaflets fuse at a series of points (inset, arrows) to form a tight junction in the apical portion of the junctional complex. Basal to this zonula occludens, there are a series of fusiform expansions of the intercellular space (F) separated by tight junctions (TJ). Throughout the length of this junctional complex, densely staining particulate or finely fibrillar material (DM) is accumulated on both cytoplasmic leaflets. (Scale: 1000A)

Fig. 2. Junctional complex at the endolymphatic surface (E) of an outer hair cell (OHC) in the second row and a supporting cell (SC) in the cat. The elements of the junctional complex including tight junctions (TJ), fusiform expansion of the intercellular space (F), and densely staining cytoplasmic material (DM) are similar to that found in the human. (Scale: 1000A)



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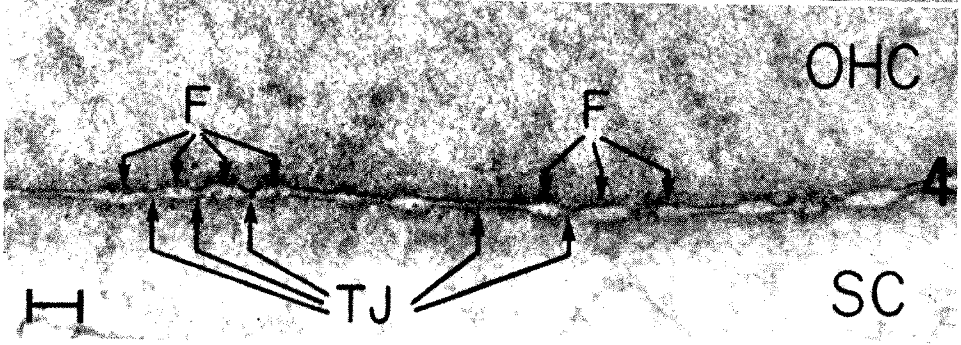

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METHODS AND MATERIALS

Cats were anesthetized by intraperitoneal injection of pentobarbital. The arterial system was perfused via the ascending aorta with normal saline followed by 2% glutaraldehyde in 0.1 M phosphate buffer at pH 7.4. The middle ears were exposed, and the scalae vestibuli and tympani perfused with the same fixative via the oval and round windows. The temporal bones were removed and immersed in the same fixative overnight at 4 C. A small opening was made at the cochlear apex to insure adequate exposure to the fixative. The cochlea was washed in 0.1 M phosphate buffer for two hours and postfixed in 2% osmium tetroxide for two hours. The otic capsule was then thinned, and the organ of Corti exposed while immersed in distilled water. Portions of the organ of Corti were removed and stained *en bloc* in 2% uranyl acetate in distilled water for three hours at 4 C. The tissue was then dehydrated in graded alcohols, rinsed in propylene oxide, and embedded in Epon® mixture.

The human organ of Corti was obtained from a 64-year-old male who died of a cardiomyopathy. The otologic history was of excellent hearing until death. However, no audiogram was available. Serial sections of the contralateral temporal bone revealed a normal organ of Corti with normal hair cell and neuronal populations. Initial fixation was achieved two hours after death by perfusion of the scalae vestibuli and tympani with 2% glutaraldehyde in 0.1 M phosphate buffer at pH 7.4. The temporal bones were immersed in the same fixative overnight.

The otic capsule was skeletonized with a surgical drill. Decalcification was achieved in 0.1 M EDTA and 2% glutaraldehyde in 0.1 M phosphate buffer at 4 C over three months after the technique of Baird *et al.*[17] The otic capsule and organ of Corti were then cut with a razor blade, washed in 0.1 M phosphate buffer, and postfixed in 2% osmium tetroxide in 0.1 M phosphate buffer for two hours. After a brief rinse in distilled water, the tissue was stained *en bloc* with 2% uranyl acetate in distilled water for three hours, dehydrated in graded alcohols, rinsed in propylene oxide, and embedded in Epon® mixture.

For the freeze-fracture preparation, tissue was obtained in the same manner. Fixation in aldehyde was limited to 30 minutes, and the tissue was then washed in 0.1 M phosphate buffer, immersed in 20% glycerol in buffer for one hour, and quick frozen in liquid Freon®.

Freeze fracturing and platinum and carbon shadowing were performed with a Balzer's apparatus.[18] Sections and replicas were examined in the Siemen's Elmiskop 1.

RESULTS

Endolymphatic Junctional Complex. A junctional complex, consisting of tight junctions and desmosomal junctions (macula adherens, zonula adherens), joined the cells of the organ of Corti at the lumenal (endolymphatic) surface in both cat and human. For purposes of description, the junctional complex was considered to be the entire series of surface membrane specializations (tight junctions, desmosomes, gap junctions) at the endolymphatic surface of hair and supporting cells. This complex extended from the free surface of these cells to approximately the basal extent of the cuticular plate. The junctional complex was subdivided into apical and basal portions. The apical portion, which will be more fully described, refers to a series of points of fusion of the limiting membranes approximately 200A apart which formed a tight junction. The structure of this apical portion of the junctional complex between apposed hair and supporting cells is similar to that seen between apposed supporting cells. The basal portion extended from the basal limit of the apical portion to the basal limit of the junctional complex. There were significant differences between the basal portion of the junctional complex seen between apposed supporting cells and that seen between apposed hair and supporting cells. No significant differences were found between the junctional complexes in the inner and outer hair cell areas or between those

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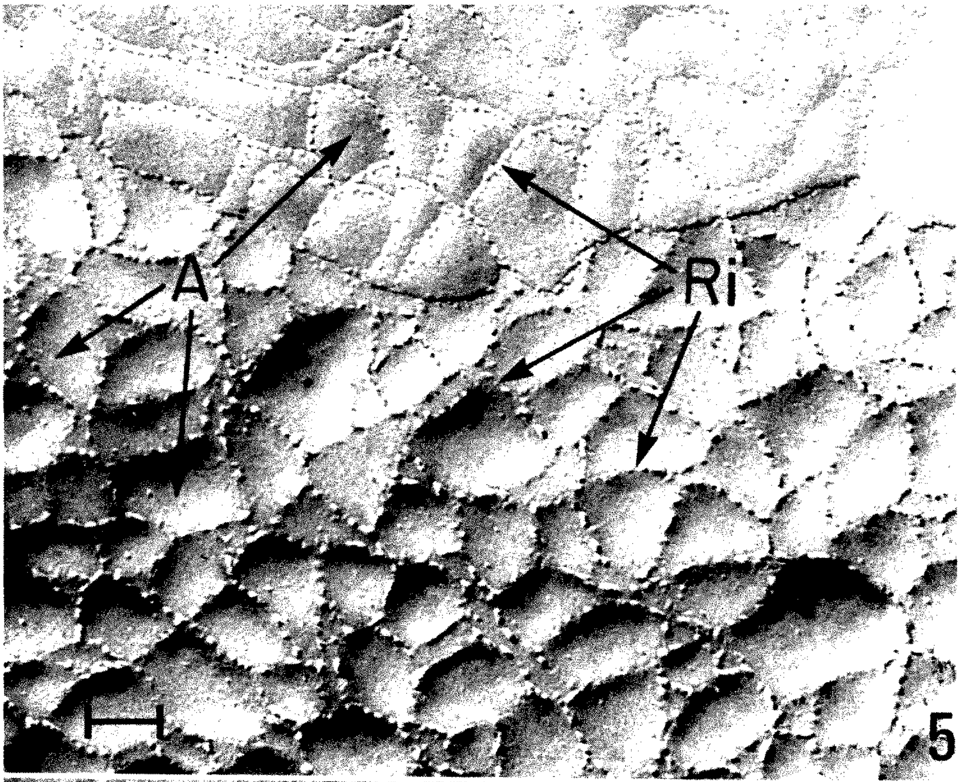
Fig. 3. Section in a plane parallel to the reticular lamina in the basal portion of the endolymphatic junctional complex in the outer hair cell area of the cat (See Fig. 11 for diagrammatic representation of the plane of section). The rootlets (R) of stereocilia clearly differentiate the outer hair cells (OHC) from supporting cells (SC). The fusiform expansions of the intercellular space (F) characterize the entire interface between hair and supporting cells at this level and differ from the longer areas of expansion of the intercellular space typical of a zonula adherens (ZA) seen between adjacent supporting cells. (Scale: 1000A)

Fig. 4. Fusiform expansion of the intercellular space (F) between an outer hair cell (OHC) and supporting cell (SC) in the basal portion of the junctional complex of the cat. Between the areas of expansion, the outer leaflets fuse to form tight junctions (TJ). (Scale: 1000A)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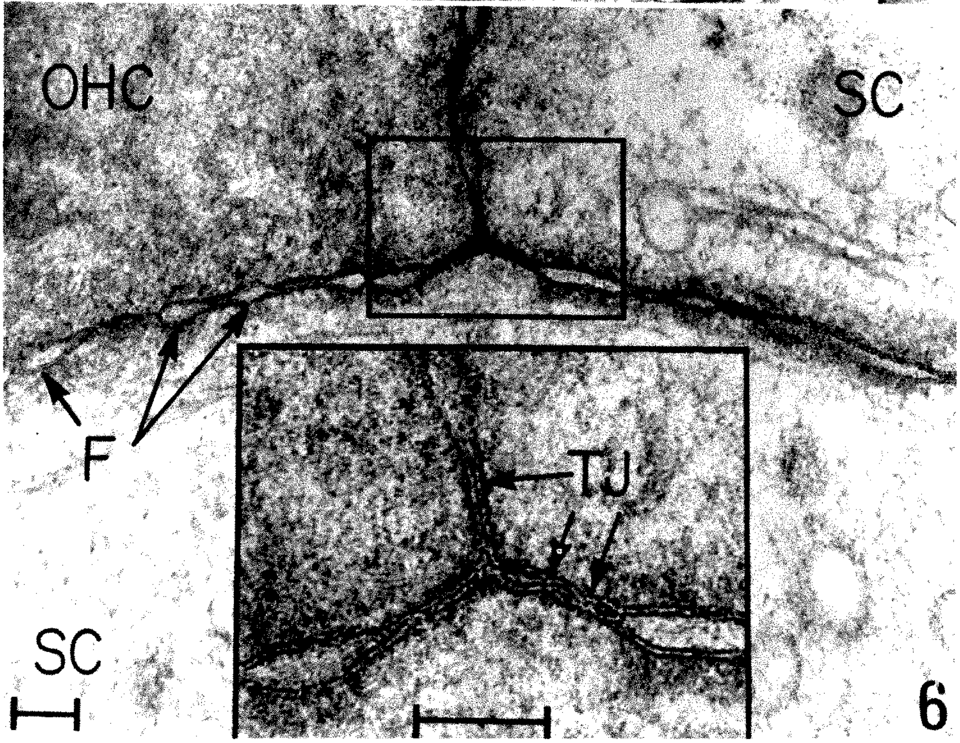
OHC
SC
F
TJ
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of cat and human. This nomenclature is summarized in Figure 11.

Junctional Complex between Hair Cells and Supporting Cells. At the endolymphatic surface in the apical portion of the junctional complex, the outer leaflets of the limiting membranes of apposed hair and supporting cells were fused at a series of points approximately 200A apart and extending to a depth of approximately one micron from the endolymphatic surface (Figs. 1 and 2). Below this level in the basal portion of the junctional complex, the points of fusion were more widely separated, and between the points of fusion there were fusiform expansions of the intercellular space approximately 250A wide (Figs. 1-4). These are shown to better advantage in sections parallel to the plane of the reticular lamina (Figs. 3 and 4). The fusiform expansions of the intercellular space corresponded in size to the spaces between ridges seen in freeze-fracture preparations of the endolymphatic junctional complex (Fig. 5). Along the entire length of the junctional complex, there was an accumulation of densely staining finely fibrillar and particulate material apposed to the inner leaflets of both hair and supporting cells (Figs. 1-4).

At junctions between three cells, the frequency of fusion of outer leaflets was the same as that at the endolymphatic surface even in the basal portions of the junctional complex where the limiting membranes of apposed hair and supporting cells were otherwise characterized by fusiform expansions of the intercellular space (Fig. 6).

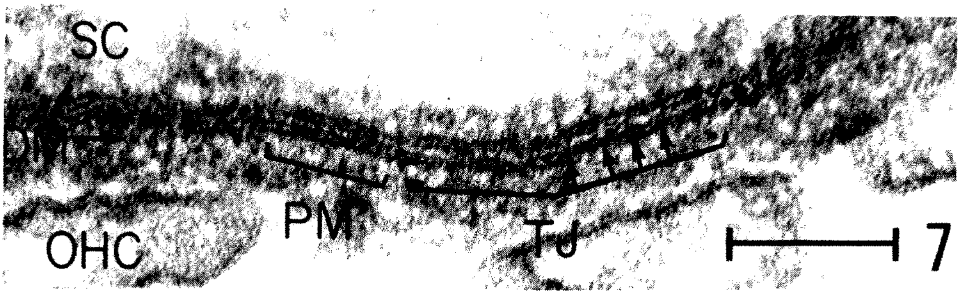
Within the junctional complex between hair and supporting cells, adjacent to tight junctions, there are areas where the inner and outer leaflets are parallel and separated by an intercellular space of approximately 20A (Fig. 7). The parallelism of both outer and inner leaflets differentiates these areas of junctional specialization from adjacent tight junctions where there is a distinct undulating appearance of the apposed membranes (Figs. 1, 6, and 7). However, unlike gap junctional specialization seen between supporting cells, there is no loss of accumulation of densely staining finely fibrillar material at each cytoplasmic leaflet.

Below the endolymphatic junctional complex, no surface membrane specialization was found between hair and supporting cells.

Junctions between Supporting Cells. The apical portion of the endolymphatic junctional complex between supporting cells (Fig. 8) is similar to that between adjacent hair and supporting cells. However, the basal portion of the junctional complex is quite different. In place of the fusiform expansion of the intercellular space seen between apposed hair and supporting cells, there are longer areas of expansion of the intercellular space consistent with zonulae adherentes between adjacent supporting cells (Fig. 8). Also, within the junctional complex, there are several short gap junctions (Fig. 8). These are discernible even at low magnification by the conspicuous absence of the densely staining fibrillar material that is apposed to the cytoplasmic leaflets elsewhere in the junctional complex. The differences between the basal portion of the junctional complex between hair and supporting cells and that between apposed

Fig. 5. Freeze-fracture replica of the basal portion of the adlumenal junctional complex in the cat. The series of interconnecting ridges of particles (Ri) correspond to tight junctional specialization seen in thin sections where the outer leaflets of apposed limiting membranes fuse. The areas (A) enclosed by these ridges correspond in size and location to the areas of fusiform expansion of intercellular space between hair and supporting cells in thin sections. No characteristic substructure was found in these areas. (Scale: 1000A)

Fig. 6. A junction between an outer hair cell (OHC) and two supporting cells (SC) in the basal portion of the endolymphatic junctional complex of cat in a plane parallel to the reticular lamina. The outer leaflets fuse at a closely spaced series of points to form a tight junction (TJ, inset) which are much like the specialization in the apical portion of the junction complex. At the same level in the basal portion of the junctional complex, these points of fusion are more widely separated by fusiform expansion (F) of the intercellular space in junctions between two cells only. (Scale: 1000A)



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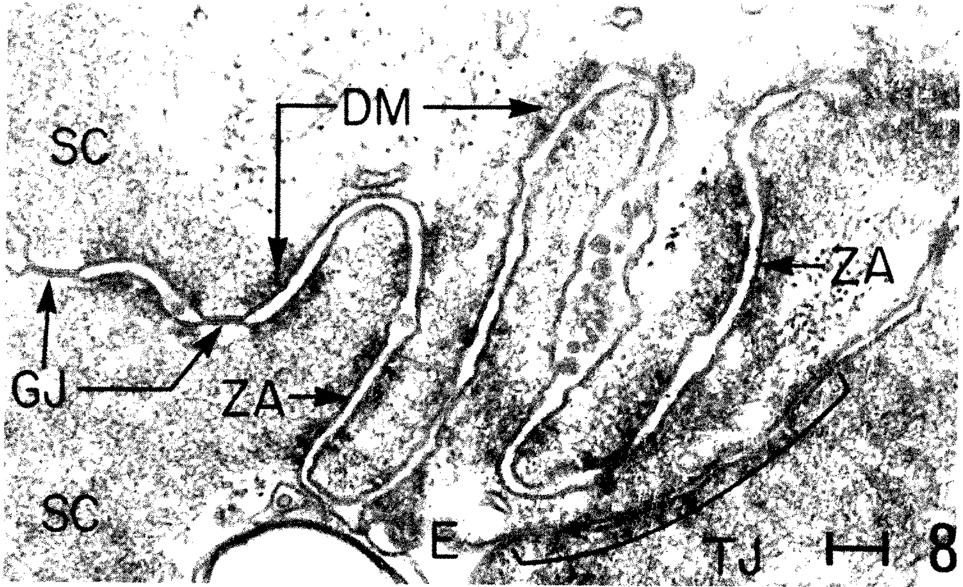

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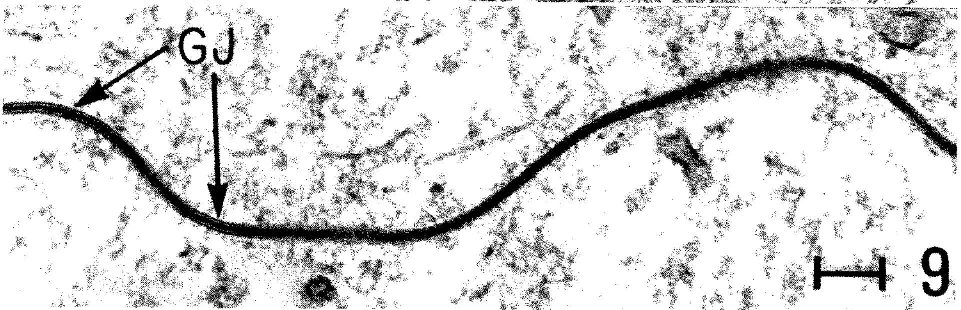

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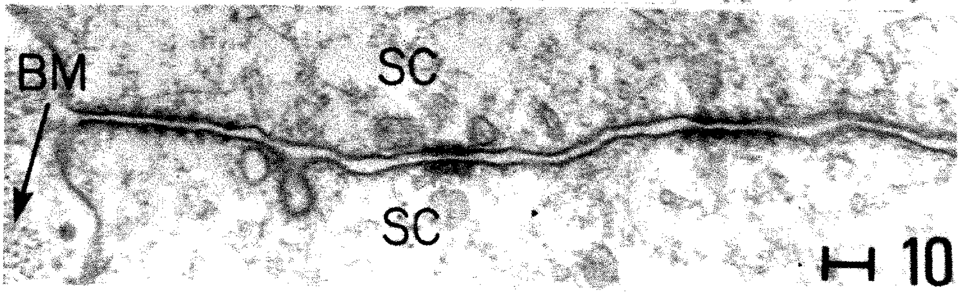

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supporting cells are readily appreciated in sections taken parallel to the reticular lamina at this level (Fig. 3).

Below the junctional complex, many long gap junctions are found between apposed supporting cells (Fig. 9). At the basilar membrane surfaces of the organ of Corti, in marked contrast to the endolymphatic surface, there are no tight junctions between apposed cells (Fig. 10).

The salient features of the junctional complexes and membrane specialization found in the neuroepithelium of the organ of Corti of cat and human are shown in a composite drawing (Fig. 11).

DISCUSSION

Tight Junctions. The essential features of the endolymphatic junctional complex described here for cat and human are common to those previously described in the alligator lizard,[13] rat,[8] and chinchilla.[14,16] In all species the intercellular space, both between apposed hair and supporting cells and between apposed supporting cells at the endolymphatic surface, is characterized by a zonula occludens. Variations in the "tightness" of the zonula occludens have been mentioned by several authors.[14-16] The absence of tight junctions at the basilar membrane surface of adjacent supporting cells is common to all species examined.

These morphological data and the results of extracellular tracer studies[19-21] suggest that the endolymphatic junctional complex acts as a permeability barrier and presumably is, at least in part, responsible for the maintenance of inner ear ionic gradients.[22] In contrast, at the basilar membrane surface of the organ of Corti, there is no anatomical finding consistent with a permeability barrier between perilymph of the scala tympani and the fluid in the spaces of Nuel. This is also in agreement with extracellular tracer studies[19-21] which demonstrate free passage of molecules from the scala tympani into the spaces of Nuel.

Desmosomal Junctional Specialization. Gilula[1] has simplified the nomenclature of several junctional specializations with similar ultrastructural characteristics. The zonula adherens (intermediate junction) and macula adherens (desmosome) are both considered to be specializations of attachment and hence "desmosomal." Little mention is made of desmosomal attachments in the organ of Corti in recent studies employing the freeze-fracture technique[14-16] probably because there is little to distinguish the zonula adherens from areas of nonjunctional membrane in this technique.[23] Although both the zonula adherens and macula adherens are thought to subserve the function of attachment between apposed cells, the

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Fig. 7. Radial section through the apical portion of the adlumenal junctional complex of an apposed outer hair cell (OHC) and a supporting cell (SC) in the human. The tight junctional specialization (TJ) is characterized by an undulating limiting membrane and a series of points of fusion of the outer leaflets (arrows). Adjacent to the segment of tight junctional specialization is a short segment characterized by parallel membrane leaflets (PM) separated by a uniform intercellular space of approximately 20A. Densely staining material (DM) is found apposed to the cytoplasmic leaflets in both segments. (Scale: 1000A)

Fig. 8. Endolymphatic junctional complex between two supporting cells (SC) in the outer hair cell area of the human seen in radial section. Tight junctional specialization (TJ) is found at the endolymphatic surface (E). In the basal portion of the junctional complex, there are large areas of expansion of the intercellular space consistent with a zonula adherens (ZA). Within the junctional complex are short gap junctions (GJ). Note that the cytoplasmic densely staining material (DM) is conspicuously absent at gap junctions in contrast to adjacent tight junctional or desmosomal specialization. (Scale: 1000A)

Fig. 9. Below the junctional complex, adjacent supporting cells, here in the outer hair cell area of the human, are joined by very long gap junctions (GJ) characterized by parallel membrane leaflets and a uniform intercellular space of approximately 20A. (Scale: 1000A)

Fig. 10. At the basilar membrane (BM) surface of adjacent supporting cells (SC), here in the outer hair cell area of the human, the intercellular space is widely patent. No tight junctions are found. (Scale: 1000A)

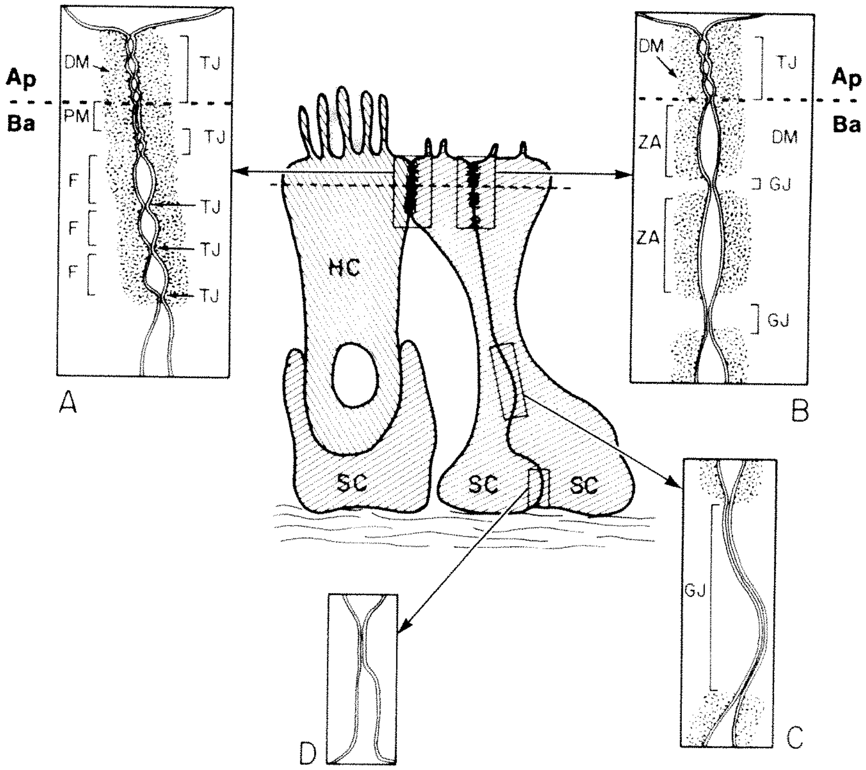

Fig. 11. Diagrammatic representation of the ultrastructural features of the intercellular membrane specialization between hair (HC) and supporting cells (SC) in the cat and human. The dashed line illustrates the plane and level of section comparable to Fig. 3.

A) Endolymphatic junctional complex between apposed hair and supporting cells. The junctional complex is subdivided into apical (Ap) and basal (Ba) portions. In the apical portion (Ap) of the complex, the outer leaflets fuse in a series of points to form a tight junction (TJ). In the basal portion (Ba) of the complex, the tight junctional fusions are more widely separated by fusiform expansion (F) of the intercellular space consistent with the membrane specialization of attachment (desmosome). Adjacent to areas of tight junctions are small areas where the apposed membrane leaflets are parallel (PM) and are separated by an intercellular space of approximately 20A. However, densely staining intercellular material (DM) is not interrupted in these areas (PM) as it is at gap junctions between supporting cells (See B & C). Compare Figs. 1, 2, & 7.

B) Endolymphatic junctional complex between apposed supporting cells. The junctional complex is subdivided into apical (Ap) and basal (Ba) portions. In the apical portions (Ap) of the complex, the outer leaflets fuse at a series of points to form a tight junction (TJ) similar to that found between apposed hair and supporting cells. In the basal portion (Ba) of the junctional complex, the expansions of the intercellular space are characteristic of a zonula adherens (ZA). Small gap junctions (GP) are found within the junctional complex. The densely staining material (DM) at the cytoplasmic leaflet found elsewhere within the junctional complex is absent at the gap junctions. Compare Fig. 8.

C) Long gap junctions (GJ) are found between apposed supporting cells below the endolymphatic junctional complex. Compare Fig. 9.

D) The intercellular space between adjacent supporting cells at the basilar membrane surface is widely patent. No tight junctions are present, although gap junctions may be found in this area as shown. Compare Fig. 10.

ultrastructure is quite distinct. The zonula adherens extends around the circumference of the cell while the macula adherens is limited to a small area between cells. The intercellular space between the limiting membranes in both types of specialization is expanded to approximately 250A, and densely staining finely fibrillar material is accumulated at the cytoplasmic leaflets in both. However, unlike the zonula adherens, in the macula adherens dense plaques are found parallel to the inner leaflets within the cytoplasm of apposed cells, and also a dense central stratum is frequently seen in the intercellular space. The similarity and yet pleomorphism of these structures are pointed out by Gilula,[1] and since at the present time both are considered to be specializations of attachment, the single term "desmosome" is used for both types of junctional specialization. The extended areas of intercellular expansion seen in junctional complex between adjacent supporting cells fulfills the criteria for the zonula adherens. The smaller fusiform expansions of intercellular space between hair and supporting cells at the same level share some of the characteristics of both the macula and zonula adherens but is not typical of either specialization. Until more is known about the functional implications of these variations, it is well to adopt the term "desmosome" for both types of junctional specialization.

A difference between the basal portions of the junctional complex between hair and supporting cells and adjacent hair cells is also described by Gulley and Reese.[14]

Gap Junctions. This recently described junctional specialization serves as a site where molecules can pass from the cytoplasm of one cell into that of an adjacent cell,[6] and also the site of electric coupling between cells so joined.[7] Gap junctions have been found between apposed supporting cells in the auditory neuroepithelium of the lizard,[13] guinea pig,[15] and chinchilla.[14,24] The findings reported here in cat and human are in accord in this respect with previous reports. The functional significance of this implied coupling between supporting cells is unknown.

Gap junctions have been described between apposed hair and supporting cells in the lizard.[13] This was correlated with neurophysiologic data[25] suggesting electrical coupling between hair and supporting cells. Gap junctions between hair and supporting cells have not been found in the mammal,[14,24] although Gulley and Reese[14] have described aggregates of small particles with the same size and spacing as seen in gap junctions interposed between the ridges of tight junctions on the cytoplasmic leaflets of both hair and supporting cells in freeze-fracture preparations of the organ of Corti of the chinchilla. However, these authors pointed out that not all morphological criteria for a gap junction were met in these areas, and hence no firm statement concerning the presence or absence of gap junctions between hair and supporting cells could be made.

Although junctional specialization typical of the gap junction was found between hair and supporting cells in the lizard,[13] no such clear examples of gap junctional specialization were found in either cat or human. However, within the junctional complex in both species, there were short lengths of parallel membrane leaflets separated by a 20A gap interposed between tight junctions between hair and supporting cells (Fig. 7). Although this membrane specialization is consistent with the gap junction, an accumulation of dense material was found juxtaposed to the cytoplasmic leaflets of both cells, a finding inconsistent with gap junctional specialization found in other epithelia,[1] with that found between supporting cells in the auditory neuroepithelium,[13,14,26] and that seen in gap junctions between hair and supporting cells in the lizard.[13] Nevertheless, as with specialization of attachment, structural pleomorphism has been described in gap junctions,[1] and it remains to be seen if these areas of specialization, suggestive but not typical of gap junctions, between hair and supporting cells in the mammal serve as sites of electric coupling between these cells.

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Ann Otol 87:1978

PRIMARY MALIGNANT LYMPHOMA OF THE PARANASAL SINUSES

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SUMMARY — A case of primary malignant lymphoma of the paranasal sinuses is presented. The patient, a 56-year-old white man, had a good response to Cobalt 60 therapy. A review of the literature reveals that this rare tumor occurs predominantly in older individuals, and that the chance for survival is good when radiation has been administered.

Malignant lymphoma of the paranasal sinuses is an extremely rare condition. Gall and Mallory[1] describe sinus manifestations in only two of 618 well-documented cases of lymphoma. Eichel *et al*[2] found only 33 patients with primary nasal and sinus lymphoma seen at the Mayo Clinic between 1933 and 1962.

Because of its rarity, two important questions arise when a sinus lymphoma is encountered. What is the best form of therapy for this condition? What is the prognosis when compared to other forms of lymphoma? In order to answer these questions, we wish to present the following typical example of the disease.

CASE REPORT

A 56-year-old white male veteran was admitted to the hospital with a three-month history of a swelling over the right side of the forehead and gradual inability to open the right eye. There was no complaint of pain, diminished vision, or diplopia. Physical examination revealed a huge, rubbery nonfluctuant mass over the right frontoethmoid region, which grossly distorted the patient's facies. The right eye was displaced downward and outward. A 2 cm firm right preauricular node was also palpated. No other evidence of adenopathy was found. Biopsy of the frontal mass and material obtained after right superficial parotidectomy revealed histiocytic lymphoma (Fig. 1). Sinus films (Fig. 2) showed the disease to involve the right ethmoid, the right maxillary, and both frontal sinuses without bone destruction. Chest x-ray, intravenous pyelogram, bone scan, and liver scan were normal. The patient was treated with Cobalt 60 therapy through anterior and right lateral portals measuring 10 x 10 cm each, with 25 fractions in 35 overall days. After *3,000* rads had been delivered, the lymphomatous lesions had disappeared, both clinically and radiographically (Fig. 3).

DISCUSSION

The history of an asymmetric swelling of the face, as in our case, is typical of sinus lymphoma. In his series, Wang[3] found this presenting sign in approximately 50% of patients. Other common signs are facial pain, nasal obstruction with bloody or watery discharge, and lacrimation.

Is sinus lymphoma unicentric in origin or multicentric at the outset? There is as yet no clear answer. The lesion in the present case was extensive when first encountered and so of undetermined origin; however, Silva *et al*[4] reports three cases apparently unicentric. The most cogent evidence that malignant lymphomas begin unicentrically and locally is provided by autopsy studies of Gall and Mallory.[1] Among 135 cases, the lesion was completely localized in 10% of subjects; in the opinion of these investigators, malignant lymphoma should not be regarded as a systemic disease at the outset, but uni-

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From the Department of Radiation Oncology, Veterans Administration Hospital, Bronx, New York.

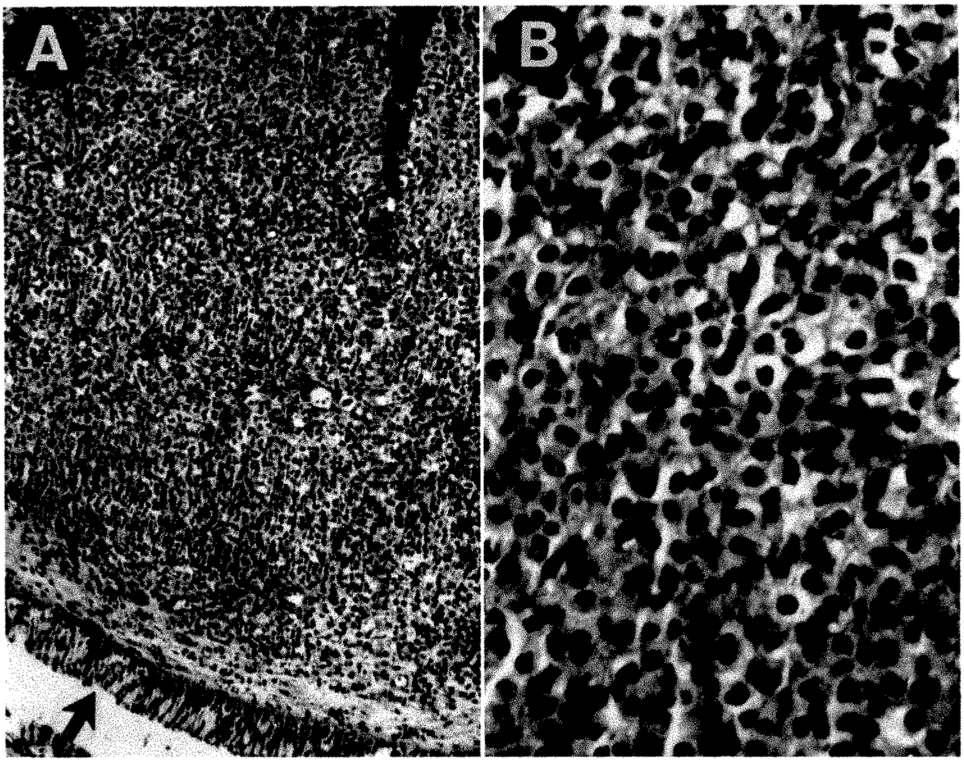

Fig. 1. A) Low power view of tissue from frontal mass shows tumor cells and epithelial lining of sinus (arrow). B) High power view reveals histiocytic character of tumor cells.

centric in origin, spreading to other locations at variable rates.

Sinus lymphoma is generally a disease of older patients of both sexes. Sofferman and Cummings[5] found 15 of 19 patients in the sixth decade of life or older and only two younger than the fourth decade, with sex distribution equally divided. Our own case, at age 56, conformed to this pattern. Histiocytic lymphoma (reticulum cell sarcoma) is commonly found among the lymphomas of older individuals. Sixteen of Sofferman's 19 cases had this histology, as did our case.

Radiation therapy is clearly the treatment of choice in sinus lymphoma, with the role of surgery limited in most cases to obtaining biopsy specimens and performing drainage operations to eliminate infections. There are no reports of systemic chemotherapy in this disorder. The optimal radiation dosage is 5,000-6,000 rads in five to six weeks.

Should "prophylactic" irradiation be given to other nodal regions in this disease entity? Two schools of thought appear to exist here. One, exemplified by Peters,[6] and Peters and Middlemiss[7] holds that unlike Hodgkin's disease, there is no merit in treating lymphatics not clinically involved. Fuller and Fletcher,[8] however, do treat the proximal lymph node areas.

The prognosis of localized malignant sinus lymphoma is good when radiation therapy has been administered. Silver[4] reports three out of four cases surviving five years. Birt[9] also reports a favorable prognosis. Although in Sofferman's series of 19 there were only five verified five-year survivors, another six were alive and free of disease for more than one year after treatment before dying of intercurrent disease or being lost to

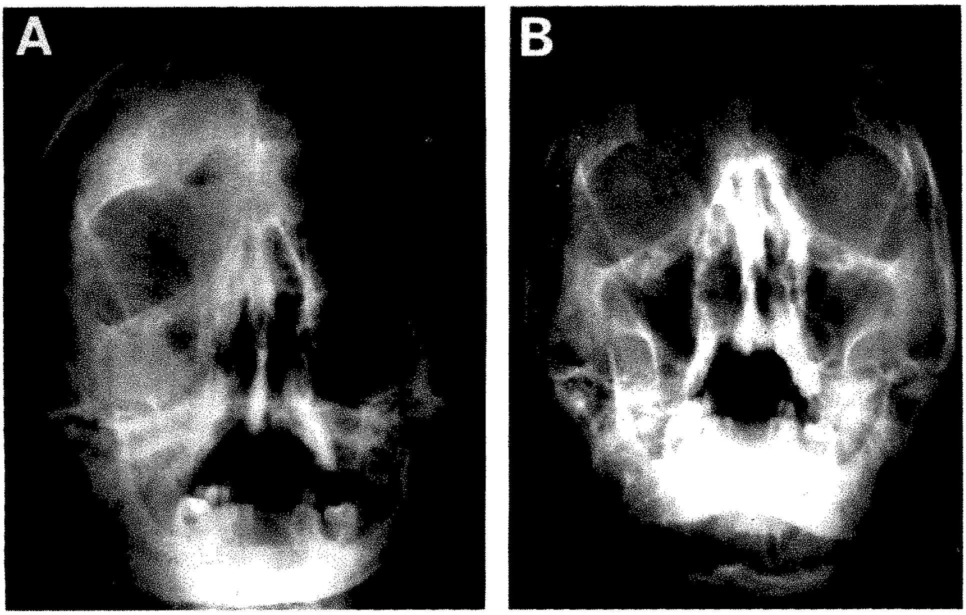

Fig. 2. A) Waters view of sinuses before radiation therapy demonstrates lymphomatous tissue opacifying the right maxillary, right frontal, right ethmoid sinuses, and part of the left frontal sinus. B) Waters view made after radiation therapy shows complete disappearance of tumor.

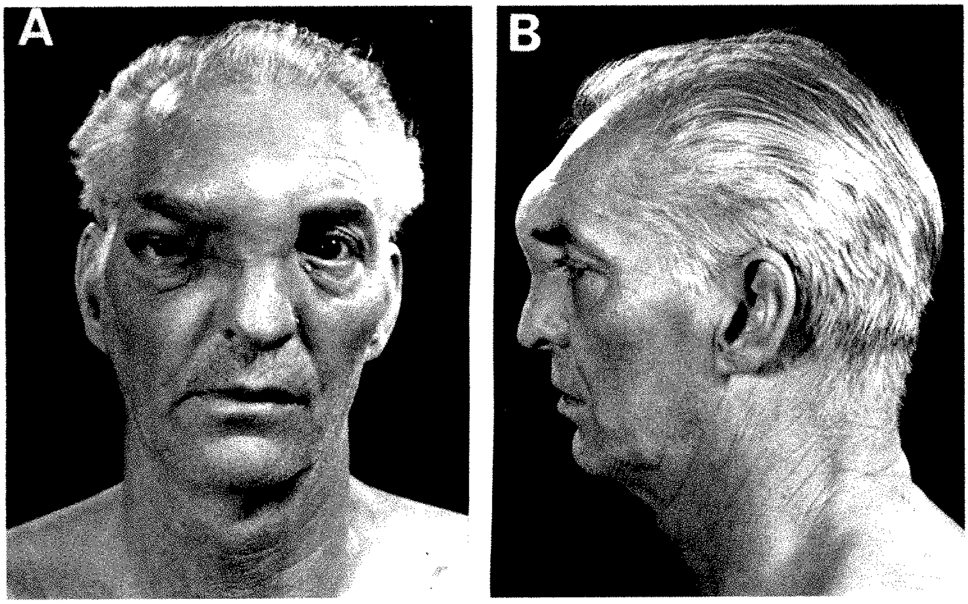

Fig. 3. A & B. Before radiation therapy, tumor mass can be seen grossly distorting patient's facies.

follow-up. A poor prognosis is suggested when the primary lesion fails to respond to radiation therapy; however, no patient in Birt's series died as a result of failure to irradiate the cervical nodes prophylactically, and such evidence as is available suggests that it may not be necessary.

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OTOSCLEROTIC INNER EAR SYNDROME

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SUMMARY — Twenty-seven patients with clinical otosclerosis and vertigo underwent stapedectomies. Vertigo improved or completely disappeared in 23 patients, indicating that stapedectomy is probably helpful. Three case reports are also presented as well as photomicrographs of temporal bones showing the focus in contact with the pars superior.

In 1966, McCabe[1] described a new entity which he called the otosclerotic inner ear syndrome. The general features include episodic vertigo and conductive hearing loss, usually unilateral. The etiology of this disorder is still obscure but, according to McCabe, it may be due to a biochemical alteration of the perilymph, perhaps by an endosteal focus of otosclerosis somewhere in the pars superior. The treatment of choice seems to be stapedectomy, and operative findings did not demonstrate saccular or utricular dilatation.[1]

Starting with the assumption that the otosclerotic inner ear syndrome is due to an endosteal focus of otosclerosis in the pars superior, we tried to substantiate McCabe's theory by reviewing temporal bone sections of patients who suffered from otosclerosis and vertigo. We also tried to establish the incidence of vertigo in patients suffering from otosclerosis by reviewing the clinical records of 400 well-documented cases of clinical otosclerosis. We will attempt to correlate the presence of otosclerotic foci in the inner ear and vertigo.

METHODS AND MATERIALS

The records of 120 patients with the histopathologic diagnosis of otosclerosis were reviewed, and the temporal bone sections prepared.*

In 85 patients the diagnosis of bilateral clinical otosclerosis was made antemortem; unilateral clinical otosclerosis was only diagnosed in 10 patients, and in 25 patients, otosclerosis was discovered postmortem (Table 1).

Out of these 120 cases of histological otosclerosis, only 12 patients (10.0%) suffered from true rotary vertigo. Out of these 12 patients, 6 had bilateral clinical otosclerosis, 4 had unilateral clinical otosclerosis, and in 2, otosclerosis was discovered postmortem. Only patients with true rotary vertigo and no fluctuation in hearing were considered in this study (Table 1).

The otosclerotic involvement was determined in all patients with vertigo (Table 2).

The first four patients in Table 2 had unilateral clinical otosclerosis and suffered from vertigo. Patients 1-4 had unilateral otosclerotic focus and moreover, this focus was in contact with the pars superior of the vestibule. Patient 2 had bilateral foci reaching the cribriform foramen of the superior vestibular nerve as well as involvement of the wall of the internal auditory meatus on the right side only (Figs. 1-3).

Patients 6 through 11 all had bilateral clinical otosclerosis and vertigo. Only patients 10 and 11 had bilateral foci in contact with the superior vestibular nerve; patient 10 had a focus around the internal acoustic canal as well (Fig. 4).

Finally, patients 5 and 12 had vertigo and neurosensory hearing impairment and only postmortem was the otosclerosis discovered. Patient 5 had a unilateral focus around the superior vestibular nerve. Patient 12 had bilateral foci, but only the right superior vestibular nerve was surrounded. These findings are summarized in Table 3. None of these temporal bones showed blockage, compression of the nerve, or degeneration of the nerve fibers by light microscopy.

CASE REPORTS

Three different cases of unilateral otosclerosis and true vertigo are reported:

Case 1. This 56-year-old woman first pre-

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TABLE 1. VERTIGO IN HISTOLOGIC OTOSCLEROSIS

	Bilaterel Clinical Otosclerosis	*Unilateral Clinical Otosclerosis*	**Undiagnosed Clinically*	*Total*
Vertigo	6	4	2	12
No vertigo	79	6	23	108
Total	85	10	25	120

*Includes Ménière's disease, perceptive hearing loss, *etc.*

sented in 1966 with a history of tinnitus and right-sided hearing loss of about 14 years' duration. She also complained of attacks of vertigo of one year's duration. She denied fluctuation of hearing and positional vertigo. Her past medical history was negative.

On physical examination her ears, nose and throat were normal. The Weber test lateralized to the right. The ENG showed slight positional nystagmus to the right; and a right directional preponderance of 13%. X-rays of the petrous pyramids were normal. The audiometric studies are shown in Figure 5.

The patient was treated as a case of Ménière's disease and placed on a vasodilator regimen for over a year. The vertigo improved, but kept on recurring for a period of eight years. Repeat audiograms failed to demonstrate any fluctuation in hearing or a deterioration in the thresholds. In 1974, polytomograms of the petrous bones were requested and showed a slight narrowing of the right oval

TABLE 2. OTOSCLEROTIC INVOLVEMENT IN PATIENTS WITH VERTIGO

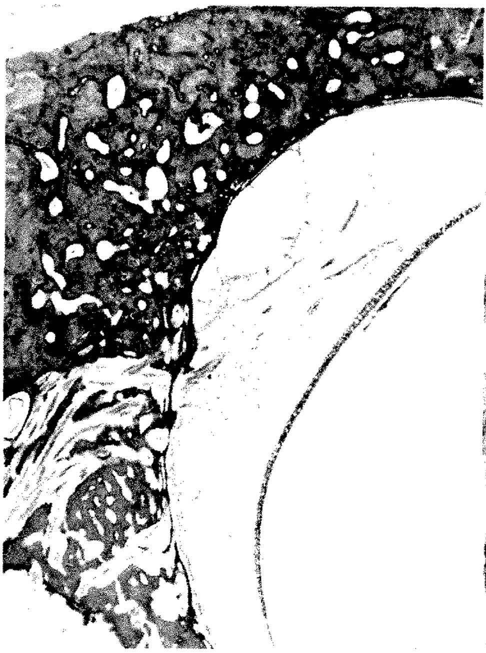
Patient	*Sex*	*Clinical Oto-sclerosis*	*Histologic Oto-sclerosis*	*Contact*	
1	M	L	L	L	Contact L only
2	F	L	B	R	Bilateral contact, also IAC R
3	F	R	B	R	Contact R only
4	F	L	L	L	Contact L only
5	F	O	B	L	Contact L only
6	F	B	B	R	Contact R only
7	F	B	B	L	Contact L only
8	F	B	B	L	Contact L only
9	M	B	B	R	Contact R only
10	F	B	B	B	Bilateral contact, also IAC R
11	F	B	B	B	Bilateral contact, surrounds SVN L
12	M	O	B	R	Contact R only

B - Bilateral
L - Left
R - Right
O - Undiagnosed clinically

Contact - Focus in contact with pars superior
IAC - Internal acoustic canal
SVN - Superior vestibular nerve

TABLE 3. CONTACT OF OTOSCLEROTIC FOCUS WITH THE PARS SUPERIOR OF THE VESTIBULE

Patients with Vertigo	*Unilateral Contact*	*Bilateral Contact*	*No Contact*	*Total*
Unilateral clinical otosclerosis	3	1	0	4
Bilateral clinical otosclerosis	4	2	0	6
Undiagnosed otosclerosis	2	0	0	2
Total	9	3	0	12



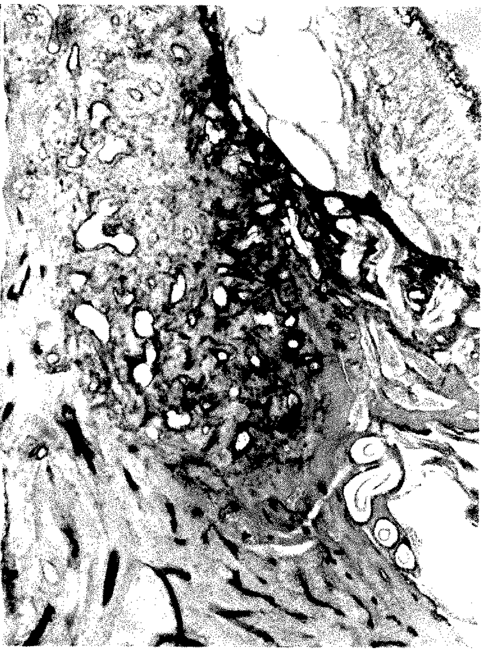
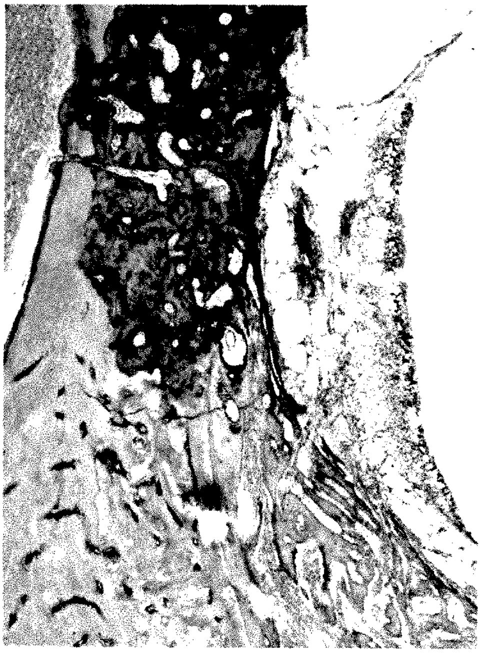


Fig. 1. Otosclerotic focus surrounding utriculoampullar nerve at base of macula utriculi. (X35)

Fig. 2. Otosclerotic focus involving cribriform area at base of macula utriculi. (X45) Note the distortion of the bony contour at base of macula.



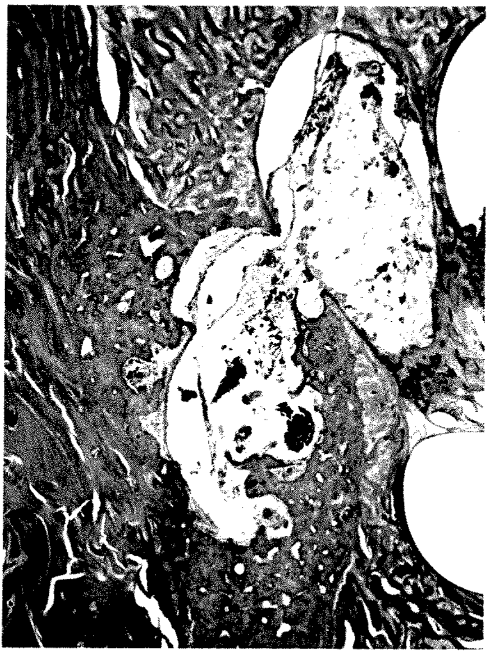


Fig. 3. Otosclerotic focus extending from fallopian canal to base of macula utriculi. (X45)

Fig. 4. Otosclerotic focus surrounding the vestibulocochlear nerve and narrowing the internal auditory meatus at the base of the cochlear modiolus. (X17.5)

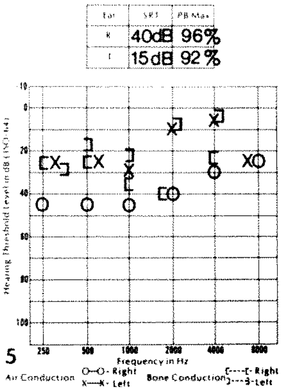


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Fig. 5. Audiogram, Case 1.

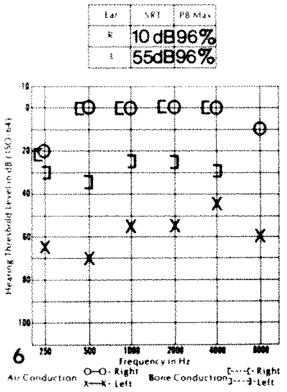

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Fig. 6. Audiogram, Case 2.

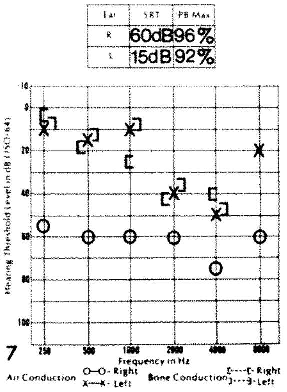

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Fig. 7. Audiogram, Case 3.

window. In January 1975 she underwent a right stapedectomy and had considerable vertigo for six weeks postoperatively, following which, the vertigo subsided completely.

Case 2. This 55-year-old lady presented in November 1973 with the chief complaint of progressive left hearing loss of seven years' duration and vertigo of two weeks' duration. Past medical history was unremarkable. On physical examination she had normal ears, nose and throat. The Weber test lateralized to the left. The ENG was normal. Polytomograms of the petrous pyramids showed bilateral cochlear otosclerosis. The audiogram is shown in Figure 6.

In January 1974 the patient underwent a left stapedectomy, following which, the vertigo disappeared by the end of the second postoperative month.

Case 3. This 50-year-old man presented in April 1974 with right-sided hearing loss of five years' duration and episodes of vertigo of two years' duration. No fluctuation of hearing. He had a past medical history of angina pectoris. Physical examination showed normal ears, nose and throat. The Weber test lateralized to the right. On ENG he had right directional preponderance of 18%. The audiogram is shown in Figure 7.

In May 1974 the patient underwent a right stapedectomy. Postoperatively the vertigo improved remarkably within three months and disappeared completely at six months.

DISCUSSION

As in the case of sensorineural hearing loss in otosclerosis, the true etiology of vertigo is still unknown and the subject is open to debate. It seems that there is no correlation between the incidence of sensorineural impairment and that of vertigo; however, a parallel could be drawn between the two conditions, since both seem to be due to affection of the VIII nerve or to changes in the end-organ.

Siebenmann[2-4] in 1899 explained "Ménière's attacks" in otosclerosis on the basis of ruptures in the partition of the vestibule causing sudden changes in pressure and position. He also described the utriculoampullar nerve to be unaffected by the surrounding focus. In 1911 he proposed that toxic substances are released from the focus in the labyrinthine fluids.[2,4] This concept was also adopted by Nager in 1969[5] to explain the gradual development of sensorineural hearing loss.

Chevance *et al*[6] carried out enzymatic studies on perilymph from otosclerotic patients and demonstrated hydrolytic activity in 75% of the samples, which correlated closely with the evolution of sensorineural hearing loss. They suggeted that these enzymes play a major role in the progressive inner ear disease in otosclerosis. Further, they demonstrated a definite correlation between the presence of proteolytic enzymes in the perilymph of otosclerotic patients and that of irritable type of ENG tracings.[7]

Ruedi[8] described the presence of vascular shunts between the inner ear circulation and the adjacent otosclerotic focus, causing congestion in the labyrinthine circulation. Whether toxic substances or vascular shunts are responsible for the sensorineural hearing impairment, it is conceivable that the same mechanism could produce a vertiginous attack by affecting the vestibular end-organ as it affects the cochlea.

In none of our 12 patients could we demonstrate dilation of the endolymphatic spaces. This clearly indicates that we are dealing with an entity different from Ménière's disease.

All 12 patients had at least one focus of otosclerosis in contact with the utriculoampullar branch of the superior vestibular nerve. The focus was also in contact with the base of the macula utriculi, and at times that of the macula sacculi. Patient 6 of Table 2 had a focus protruding into the vestibule and impinging on the macula sacculi. Patients 2 and 10 demonstrate the involvement of the internal acoustic meatus with an otosclerotic focus. There was no demonstrable loss or degeneration of nerve fibers in any patient.

Thus it seems logical to assume that vertigo is related to the presence of a focus of otosclerosis in contact with the pars superior of the vestibule or the superior vestibular nerve. The exact mechanism is unknown, but it is conceivable that a focal loss of macular neuroepithelium could occur as hypothesized by McCabe in 1966.[1] Such a loss could be attributed to toxic substances such as those described by Siebenmann and later demonstrated by Chevance *et al,* Causse *et al,* or to Ruedi shunts, or a combination of both compounded by local ischemia and anoxia to the end-organ. Unequal neural impulses are fired into the brain when the head moves into such a position that this macular area would be stimulated. This imbalance of impulses results in vertigo. The brain responds immediately by eliminating the discharge from the corresponding contralateral macula through central inhibitory channels, thus self-limiting this condition.

TABLE 4. INCIDENCE OF VERTIGO IN 400 CASES OF CLINICAL OTOSCLEROSIS

	Unilateral Otosclerosis	*Bilateral Otosclerosis*	*Total*
No vertigo	174	185	359
Vertigo	26	15	41
Total	200	200	400

We tried to establish the incidence of vertigo in the presence of clinical otosclerosis. For this purpose 200 consecutive cases of clinical unilateral otosclerosis and 200 cases of bilateral clinical otosclerosis were reviewed. Only patients with true rotary vertigo and without fluctuation in hearing were selected. The incidence of vertigo in unilateral otosclerosis was 13% and 7.57% in bilateral otosclerosis. The difference is not statistically significant. The overall incidence was 10.2%. Table 4 summarizes the results.

Of these 41 patients with clinical otosclerosis and vertigo, 27 patients underwent stapedectomy. These patients were followed up to at least six months after surgery and the results are shown in Table 5. Following stapedectomy 13 out of 16 patients (81.2%) with unilateral clinical otosclerosis had improvement of their vertigo as evidenced by a history of decrease in the intensity and frequency of the attacks, or complete subsidence. Out of 11 patients with bilateral otosclerosis, ten improved after stapedectomy (99%). The overall improvement was 85.12%.

It is clear from these results that stapedectomy seems to be helpful in

TABLE 5. IMPROVEMENT OR DISAPPEARANCE OF VERTIGO FOLLOWING STAPEDECTOMY

	Improved	*Not Improved*	*Total*	*Percent*
Unilateral clinical otosclerosis and vertigo	13	3	16	81.2%
Bilateral otosclerosis and vertigo	10	1	11	99.9%
Total	23	4	27	85.1%

eliminating the vertigo associated with otosclerosis, provided coexistent Ménière's disease has been ruled out.

CONCLUSION

The otosclerotic inner ear syndrome seems to be a separate entity related to the presence of an otosclerotic focus in the vicinity of the pars superior of the posterior labyrinth. The various theories pertaining to its etiology have been reviewed and it seems that the overall incidence is 10.2%, which is much lower than some of the figures quoted in the literature (15-25% Causse *et al*)[7-9] and quite higher than McCabe's figure of 3%. The treatment of choice seems to be a stapedectomy.

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Ann Otol 87:1978

NASOPULMONARY REFLEX: EVALUATION IN THE NONPARALYZED AND PARALYZED ANESTHETIZED DOG

James H. Whicker, MD

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SUMMARY — Changes in the pulmonary mechanics of various animal species have been observed after nasal stimulation. In reviewing the methods of these studies, we found that often the respiratory patterns were not controlled well enough to permit conclusions about changes in resistance and compliance. To further investigate the possibility of a nasopulmonary reflex, we first studied the effect of nasal stimulation on pulmonary mechanics in anesthetized, nonparalyzed dogs. In this group of 35 dogs, we found that nasal stimulation typically produced marked changes in breathing patterns, a large transient increase (150%) in pulmonary airflow resistance, but no change in compliance. This response to nasal stimulation could be abolished by interrupting either the trigeminal or the vagus nerves. In an additional group of 12 anesthetized, paralyzed dogs, we found no changes in resistance or compliance after nasal stimulation. From this observation, we concluded that nasal stimulation produced changes in breathing patterns that led to alterations in resistance without an actual change in the intrinsic behavior of the pulmonary airways.

Changes in the pulmonary mechanics of various animal species have been observed after nasal stimulation.[1-4] Corn *et al*[5] demonstrated an increase in pulmonary airflow resistance in cats secondary to SO_2 irritation of the nasopharynx. Ogura *et al*[6] found an increase in pulmonary airflow resistance in dogs with surgically created nasal obstruction. Angell James and Daly[7] noted the production of apnea in dogs after intranasal stimulation with ice water. In contrast to the findings of increased airflow resistance noticed in the previous investigations, Tomori and Widdicombe[8] produced bronchodilation in cats by stimulating the nasal mucosa. Kaufman and Wright[9] reported significant increases in airflow resistance after nasal stimulation with silica particles in ten unanesthetized human subjects. Ogura and Harvey[10] noted a decrease in compliance and an increase in resistance during oral as well as nasal breathing in most human subjects who had severe nasal obstruction.

Because of these reports, the presence of a nasopulmonary reflex which affects pulmonary airflow resistance and compliance has been postulated. However, in reviewing these reports, we were impressed that in none were the pulmonary breathing patterns and volumes controlled well enough to allow accurate conclusions regarding changes in pulmonary resistance and compliance. To further evaluate the existence of a nasopulmonary reflex, we studied the changes in pulmonary mechanics after nasal stimulation in anesthetized, nonparalyzed dogs and in anesthetized, paralyzed dogs. In addition, we defined the neural pathway of the so-called nasopulmonary reflex by sectioning or stimulating the trigeminal nerves and sectioning the vagus nerves.

METHODS AND MATERIALS

Measurements were made on three groups of dogs: group 1 included anesthetized, nonparalyzed dogs before surgical section of the trigeminal or vagus nerves; group 2 included anesthetized, nonparalyzed dogs after surgical section of the trigeminal or vagus nerves; and group 3 included neurologically intact, anesthetized, paralyzed dogs. In the third group,

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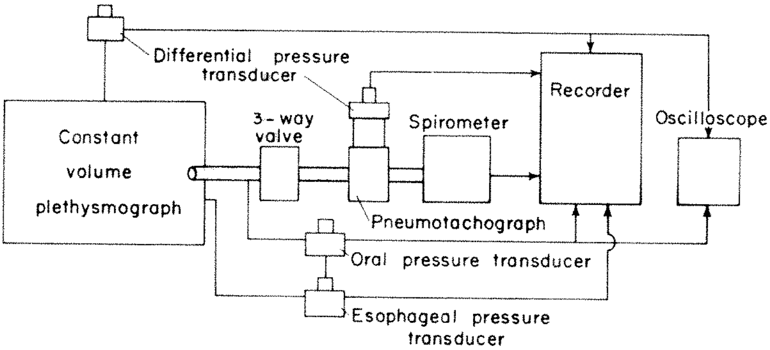
Differential pressure transducer
Recorder
Oscilloscope
Constant volume plethysmograph
3-way valve
Spirometer
Differential pressure transducer
Pneumotachograph
Oral pressure transducer
Esophageal pressure transducer

Fig. 1. Schematic diagram showing arrangement of equipment.

we first studied the responses of the anesthetized but nonparalyzed dogs. When it was apparent that these dogs responded to nasal stimulation in a manner similar to that of the dogs in group 1, we then paralyzed the group 3 dogs and stimulated the nasal mucosa during controlled ventilation.

In 35 dogs of group 1 (mean weight 16 kg), pulmonary airflow resistance, dynamic lung compliance, and thoracic gas volumes were measured before and after stimulation of the nasal mucosa. Anesthesia was induced with intravenously administered pentothal (26 mg/kg), and the dogs were intubated and placed in a plethysmograph in the left lateral position. A thermal (ice water) stimulus was applied to the nasal vestibule. By keeping the muzzles of the dogs dependent, we prevented the injected water from flowing into the nasopharynx. Ice water was chosen as the stimulus because it had been used successfully by other investigators.[1,4,7] Of the various types of stimulation with which we experimented (compressed air and mechanical), ice water seemed to be the most reliable; in addition, the use of ice water provided better control over the degree of stimulation and the area to be stimulated. The methods of determining pulmonary resistance, compliance, and thoracic gas volume were similar to those described by Gillespie and Hyatt.[11] The initial part of our investigation was conducted with a constant volume plethysmograph before we switched to the constant pressure plethysmograph utilized by Gillespie and Hyatt.[11] A diagram of the experimental apparatus is shown in Figure 1. Pressure changes in a constant volume plethysmograph were related to atmospheric pressure by a differential pressure transducer. A three-way valve enabled the airway to be occluded for thoracic

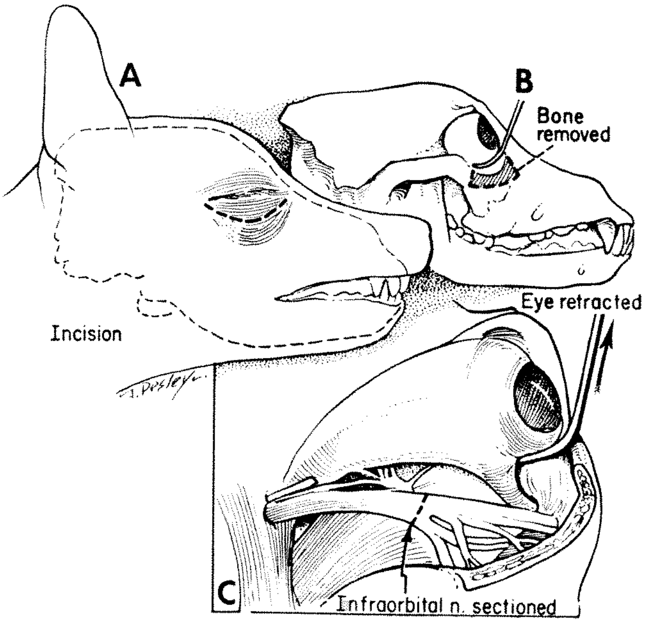

Fig. 2. Transorbital approach to sensory nerves of nose. Infraorbital incision (A). Elevation of soft tissue, permitting removal of bony rim (B). Interruption of appropriate nerves (C).

TABLE I. VALUES OF RESISTANCE AND COMPLIANCE BEFORE AND AFTER TRIGEMINAL NERVE STIMULATION(S)

	Resistance (cm $H_2O/L/s$)			*Compliance (ml/cm H_2O)*		
Dog	*Before S*	*After S*	*Change (%)*	*Before S*	*After S*	*Change (%)*
T421	3.2	6.8	+113	50	12	− 76
T521	2.4	5.6	+133	56	50	− 11
T489	2.4	4.8	+100	67	67	0
T730	1.2	6.4	+433	70	100	+ 43
T307	1.8	4.1	+128	45	110	+144
Mean	2.2	5.5	+181	58	68	+ 20

gas volume determinations. Flow was measured with a pneumotachograph.* Pressure transducers monitored oral and esophageal pressures. Volume changes were measured by a 9-liter spirometer with an attached potentiometer. A CO_2 absorber was contained within the spirometer. Signals from the four pressure transducers and the spirometer were recorded on a six-channel recorder.

The baseline or prestimulatory pulmonary flow resistance value was the mean of eight breaths calculated at a constant volume.[13] Measurements were made at the same lung volumes before and after stimulation. The baseline compliance value was the mean of eight breaths. The poststimulatory pulmonary resistance and compliance values reported represent the maximal change in resistance and compliance of any single breath after nasal stimulation.

In an additional five dogs in the first group, the nasal branches of the trigeminal nerve were exposed through a transorbital approach to allow stimulation (Fig. 2). In this group, the nerves were stimulated with a unipolar electrode, and the changes in lung mechanics were recorded. Square-wave pulses of an intensity of 4 V and a duration of 3 ms were used.

The second group of dogs was studied after surgically interrupting the trigeminal or the vagus nerves. Five dogs underwent interruption of the trigeminal nerves. Responses to nasal stimulation before neurolysis of the trigeminal nerves were recorded. The nerves were then interrupted and responses to nasal stimulation were recorded within 15 minutes after interrupting the nerves. To further ensure that denervation in itself did not alter resistance and compliance, we compared the normal day-to-day variability in resistance and compliance values in eight additional dogs before denervation, and we also obtained resistance and compliance values in sequential recordings during the week after denervation.

In five additional dogs, responses to nasal stimuli were obtained immediately before and after bilateral surgical interruption of the vagus nerves at the level of the tympanic bulla.

A third group of 12 dogs was studied to observe the changes in pulmonary mechanics in anesthetized, paralyzed dogs and to compare these results with those of the first group.

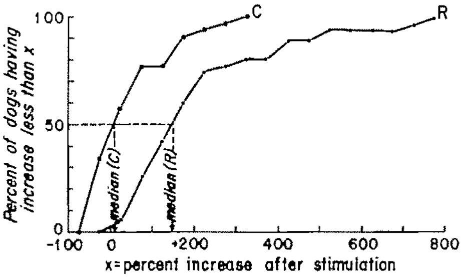

Fig. 3. Curves showing that median increase in compliance (C) after stimulation of the nonparalyzed dog was 10%. Median increase in resistance (R) was 150%.

In these studies, a constant pressure plethysmograph with an attached spirometer** was employed. The dogs in this group were anesthetized with intravenously administered pentothal (26 mg/kg), and the effects of nasal stimulation were recorded. The dogs were then paralyzed using intravenously administered succinylcholine (20 mg), and after the dogs were placed on a constant volume respirator† at the same tidal volume and rate as that prior to paralysis, the nose was stimulated using the same technique that we had employed on the nonparalyzed dogs.

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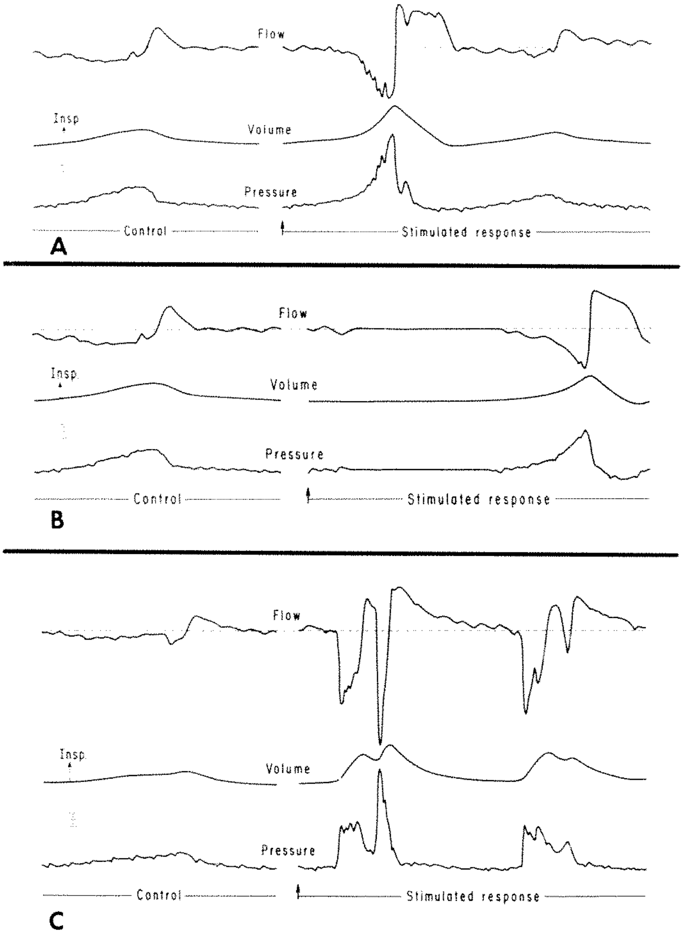

Fig. 4. A) Increase in flow, volume, and pressure for one breath with a rapid return to normal. B) Period of apnea precedes change in flow, volume, and pressure. C) Series of sneezes.

RESULTS

GROUP 1: ANESTHETIZED, NONPARALYZED DOGS BEFORE NERVE INTERRUPTION

Stimulation of Nasal Mucosa. After nasal stimulation in the 35 dogs in this group, a statistically significant ($P < 0.01$, two-tailed t test) increase in pulmonary airflow resistance occurred (Fig. 3). The median increase in pulmonary resistance for the entire group was 150%. However, the median increase in compliance of 10% for the entire group was not statistically significant.

Several patterns of breathing response to stimulation were noted in this group of dogs. The most frequent response was a sudden change in the respiratory pattern which lasted for one to three breaths before returning to normal (Fig. 4A). The response second in frequency was a brief period of apnea, followed by an altered respiratory pattern of from one to three breaths (Fig. 4B). The third and least frequent response was a series of sneezes which lasted for 5 to 15 breaths (Fig. 4C).

Stimulation of Nasal Branches of Trigeminal Nerve. Pulmonary resistance increased in all dogs, with a significant mean increase of 181% ($P < 0.05$, two-tailed t test, Table I). Compliance decreased slightly in two dogs, increased in two, and was unchanged in one. The

TABLE II. VALUES OF RESISTANCE AND COMPLIANCE BEFORE AND AFTER STIMULATION(S) OF THE DENERVATED NASAL MUCOSA

	Resistance (cm H_2O/L/s)			*Compliance (ml/cm H_2O)*		
Dog	*Before S*	*After S*	*Change (%)*	*Before S*	*After S*	*Change (%)*
T421	2.7	2.7	0	20	17	−15
T521	3.2	3.0	− 6	80	90	+13
T489	2.7	3.1	+15	81	71	−12
T730	3.4	3.4	0	61	72	+18
T307	2.5	2.5	0	56	56	0
Mean	2.9	2.9	+ 1.8	60	61	+ 0.8

mean change in compliance was not statistically significant. The same breathing pattern changes occurred in this group that occurred in the first subgroup of neurologically intact dogs.

GROUP 2: ANESTHETIZED, NONPARALYZED DOGS AFTER NERVE INTERRUPTION

Stimulation of Nasal Mucosa After Ablating Nasal Branches of Trigeminal Nerve. Stimulation of the nasal mucosa in five dogs after sectioning the nasal branches of the trigeminal nerve did not significantly alter resistance and compliance (Table II). Long-term effects of denervation of the eight dogs showed no significant change in pulmonary resistance or compliance.[18]

Stimulation of Nasal Mucosa After Cervical Vagotomy. In this group, we found that interruption of the vagus nerves alone decreased the respiratory rate and increased the total volume. After nasal stimulation, pulmonary resistance decreased slightly in four dogs and was unchanged in the remaining dog. The mean decrease in pulmonary airway resistance of 10% after stimulation was not statistically significant. Compliance was unchanged in four dogs and increased in one. The mean increase in compliance of 4% was not statistically significant (Table III).

GROUP 3: ANESTHETIZED, PARALYZED DOGS (NEUROLOGICALLY INTACT)

Stimulation of Nasal Mucosa. All 12 dogs in this group were stimulated before and after paralysis. Before paralysis, the dogs demonstrated the changes typical of the nonparalyzed dogs in group 1. Fixed respiratory patterns were then imposed on the dogs by paralyzing them with intravenously administered succinylcholine and placing them on a constant volume respirator. After nasal stimulation, the dramatic changes in respiratory patterns seen in the group of nonparalyzed dogs did not occur in the paralyzed dogs. Furthermore, there was no statistically significant change in pulmonary resistance or compliance in this anesthetized, paralyzed group (Table IV). The higher baseline resistances

TABLE III. VALUES OF RESISTANCE AND COMPLIANCE BEFORE AND AFTER STIMULATION (S) OF MUCOSA OF VAGOTOMIZED DOGS

	Resistance (cm H_2O/L/s)			*Compliance (ml/cm H_2O)*		
Dog	*Before S*	*After S*	*Change (%)*	*Before S*	*After S*	*Change (%)*
T503	1.0	0.9	−10	65	65	0
T306	2.3	2.0	−13	42	42	0
S70	2.8	2.1	−25	22	26	+18
T148	3.6	3.6	0	55	55	0
T222	3.1	3.0	− 3	72	72	0
Mean	2.6	2.3	−10	51	52	+ 4

TABLE IV. VALUES OF RESISTANCE AND COMPLIANCE IN PARALYZED DOGS BEFORE AND AFTER STIMULATION(S)

	Resistance (cm $H_2O/L/s$)			*Compliance (ml/cm H_2O)*		
Dog	*Before S*	*After S*	*Change (%)*	*Before S*	*After S*	*Change (%)*
1	4.2	3.7	−12	76	77	+1
2	4.9	5.1	+4	69	67	−3
3	3.4	3.5	+3	37	36	−3
4	3.0	2.9	−3	60	61	+2
5	4.2	4.0	−5	64	65	+2
6	6.0	5.9	−2	49	47	−4
7	3.9	4.1	+5	69	67	+3
8	5.2	5.0	−4	85	84	−1
9	5.2	5.1	−2	84	84	0
10	8.2	8.3	+1.2	74	73	−1
11	6.2	6.3	+1.6	30	40	+33
12	5.3	5.0	−6	89	91	+2
Mean	4.98	4.91	−1.6	68.7*	48.4*	−.18*
SD	1.41	1.46	4.87	15.76*	16.34*	2.40*

*Note compliance data from dog 11 omitted from calculations of mean (SD).

seen in Table IV reflected the fact that a smaller endotracheal tube was used. Four additional dogs were studied using a larger endotracheal tube. Resistance in these dogs averaged 1.85 cm $H_2O/L/s$ before stimulation and 1.49 cm $H_2O/L/s$ after stimulation. This change was not statistically significant.

DISCUSSION

It is well known that increases in airway flow can lead to changes in resistance without alterations in the intrinsic behavior or the size of the intrapulmonary airways. Such changes reflect the nonlinearity of the pressure-flow relationships of the lung. Thus, in Figure 5, measurement (*a*) taken at resting respiratory flow will give a lower resistance value than measurement (*b*) taken at a higher flow rate even though the pressure-flow relationships of the lung are unaltered.

Similarly, changes in volume can alter compliance[14] due to the nonlinearity of the pressure-volume characteristic of the lung. Therefore, to avoid these problems, we imposed a fixed respiratory pattern on the dogs. This was accomplished by paralyzing the dogs and placing them in a constant pressure plethysmograph. A paralyzing agent such as succinylcholine should not affect bronchoconstriction or bronchodilation that is mediated by smooth muscle.[15] True resistance and compliance changes resulting from alterations of

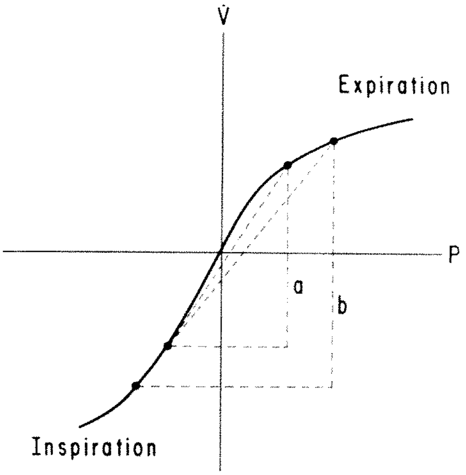

Fig. 5. Pressure-flow curve during inspiration and expiration. Depending on the segment of an isovolume pressure flow curve to be measured, the resistance will vary, although the curve remains the same.

lung mechanics secondary to a nasopulmonary reflex would be expected in spite of respiratory muscle paralysis.

Changes in respiratory patterns consistently occurred in anesthetized, nonparalyzed dogs after nasal stimulation. Nonparalyzed dogs that demonstrated dramatic changes in resistance also tended to have increases in respiratory flow. However, paralyzed dogs with fixed flow rates exhibited no changes in airway resistance. Because succinylcholine would not be expected to interfere with smooth-muscle-mediated bronchoconstriction or bronchodilation, our data suggest there is no nasopulmonary reflex in anesthetized dogs that directly affects airway resistance or compliance. We do, however, believe that there is a nasorespiratory reflex which affects respiratory breathing patterns. This reflex could be initiated by stimulating the afferent nasal branches of the trigeminal nerves and was abolished by surgically sectioning the trigeminal or the vagus nerves.

Although the afferent limb of this nasorespiratory reflex appears to be the trigeminal nerves, the role of the vagus nerves is less certain. Investigators have demonstrated that the vagus nerves exert powerful control over depth and rate of breathing.[16-18] Vagal reflexes appear essential for mediating the self-regulation of respiration. Bishop and Bachofen[19] believed that "afferent vagal impulses influence the division of labor between the inspiratory and expiratory muscles to achieve better mechanical efficiency of the respiratory pump." In our present study, interruption of the vagus nerves may have prevented both afferent messages to the respiratory center and efferent messages to the muscles controlling respiratory patterns.

A thorough search of the literature revealed that most other investigations of nasopulmonary reflexes were done in anesthetized, nonparalyzed animals. Because possible variations in respiratory patterns were not controlled in those studies, the authors' conclusions that pulmonary resistance and compliance change after nasal stimulation are subject to doubt. We conclude there are no unequivocal experimental data which indicate that mechanical or chemical stimulation of the nasal mucosa alters pulmonary mechanics in the anesthetized dog.

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Reprints — Eugene B. Kern, MD, Mayo Clinic and Mayo Foundation, Rochester, MN 55901.

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THE DEAFNESS RESEARCH FOUNDATION

The Deafness Research Foundation invites applications for 1979 grant support of research projects directed to any aspect of the ear; e.g., investigation of function, physiology, biochemistry, genetics, anatomy or pathology. Grant support is given for one year in an amount that cannot exceed $10,000, but can be renewed for one or two additional years for meritorious projects.

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FIFTH BRITISH ACADEMIC CONFERENCE IN OTOLARYNGOLOGY

The Fifth British Academic Conference in Otolaryngology will be held July 22-27, 1979, at the University of Birmingham (U.K.). Master will be Sir Geoffrey Bateman, MA, FRCS. This conference has academic and scientific programs with distinguished international contributors to discuss a wide range of modern developments within the specialty.

Morning plenary sessions will be held with papers from invited speakers. Open panel discussions will be a significant feature and instructional sessions will also take place as well as audiovisual programs. Finally there will be a scientific and trade exhibition.

For further information and application forms write: V. Hammond, FRCS, 55 Harley Street, London WI, England.

Ann Otol 87:1978

COMPARISON OF FIVE TYPES OF TRACHEOSTOMY TUBES IN THE INTUBATED TRACHEA

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PEDRO S. TOLEDO, PhD
KANSAS CITY, KANSAS

SUMMARY — Recognition of excessive cuff pressures as a major factor in tracheal injury has prompted the development of different types of cuffed tracheostomy tubes. Five brands of tracheostomy tubes in common use are evaluated in anesthetized adult dogs. Visualization of interior tracheal conditions during spontaneous and positive pressure ventilation permits a dynamic study of the trachea and its interaction with each tube under varying conditions. The relationship between intracuff pressure and cuff-tracheal wall pressure is analyzed for each tube. The selection of the proper tracheostomy tube for a given clinical situation should consider: 1) the cuff pressure necessary to achieve minimal leak, 2) torque transmission, 3) the ability to monitor cuff-tracheal wall pressure as a function of intracuff pressure, and 4) simplicity of design for optimum clinical use. Tracheal expansion occurs in a predictable fashion in response to different stimuli. However, the role of expansion in the susceptibility of this organ to injury remains to be investigated.

The role of the otolaryngologist has classically included airway management and repair of tracheal injuries. This role has broadened to include other specialties since the advent of endotracheal intubation and positive pressure ventilation (PPV). However, there continues to be a demand for airway management by tracheotomy where the endoral approach is not feasible. The recent recognition that tracheal damage by cuffed tubes is directly related to pressure applied has become a stable concept in airway management, both in PPV and spontaneous ventilation.[1] If Otolaryngology is to maintain its role in the management of airway problems and tracheal disease, our knowledge must expand in this area. The otolaryngologist must assume the responsibility for prevention as well as for repair of iatrogenic tracheal injury. Portions of this study may seem unnecessarily detailed. However, attention to detail and specifics of tube size and cuff volume will be shown to be as necessary a part of the otolaryngologist's armamentarium as is the knowledge of the appropriate size bronchoscope needed for an infant. Knowledge of these details is critical during this current period of development, since many undesirable devices remain in hospital storerooms while others are being distributed without adequate testing and documentation of injury potential.

The use of PPV and prolonged tracheal intubation has increased considerably in recent years in clinical medicine. This has prompted the development of numerous intubation devices, all claiming to prevent tracheal injury. Every mechanical device has certain physical characteristics which are determined by its construction. The tracheostomy tubes evaluated in this study differ in their construction, and all claim to reduce trauma to the trachea.

The following *in vivo* study in dogs evaluates certain characteristics of five different tracheostomy tubes commercially available today. The characteristics evaluated are those which the authors feel may play an important role in causing tracheal injury. These charac-

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From the Department of Otorhinolaryngology, University of Kansas Medical Center, Kansas City, Kansas. This study was supported by funds from NINDS Grant TNS 5487 CDR.

teristics are: 1) the relationship between intracuff pressure (ICP) and cuff-to-tracheal wall pressure (CTP), 2) the transmission of torque from tube connector to the tip of the tube, and 3) the CTP necessary to obtain minimal leak. The authors believe that the intelligent clinical use of an intratracheal device should take these characteristics into consideration.

The dynamic behavior of the trachea was studied by direct observation of the tracheal lumen through a telescope and by recording changes in tracheal diameter. The effects of change in tracheal diameter on the characteristics and performance of each tube are discussed.

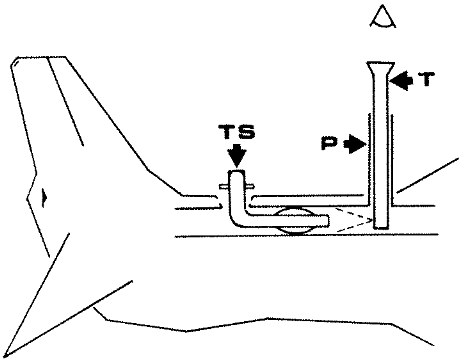

Fig. 1. An upper tracheostomy incision is preformed for insertion of the tubes (TS) under study. PVC tubing (P) is sutured to the lower stoma to provide easy insertion of the telescope (T).

METHODS AND MATERIALS

The study population consisted of ten healthy adult mongrel dogs weighing 10-12 kg. Each animal was anesthetized with intravenous sodium pentobarbital (30 mg/kg). A Bennet PR-1 respirator provided PPV when needed. A Gilson recorder and Statham pressure transducers monitored ICP, CTP, intraairway pressure and respiratory cycle.

Five types of tracheostomy tubes were evaluated: Portex with Soft Seal Cuff,* Shiley,** Bivona,† Lanz,†† and the Surgitek‡ tracheostomy tube. The tubes were provided in a full range of sizes by each manufacturer with the exception of the Shiley and Portex tubes which were obtained from supplies on hand at the University of Kansas Medical Center. A detailed description of each tube will be provided in the discussion.

Study Groups. In five animals (Group I) each of the five tube types was evaluated in random sequence in each animal. In the other five animals (Group II) a single tube brand was used in each animal, but different size tubes were used. This was done to evaluate the possible effects of different types of tubes on tracheal dilation.

A high tracheostomy was performed in each animal. Ten centimeters below the upper tracheal incision a disc of cartilage was removed from two adjacent cartilages. Care was taken to avoid excessive dissection of the trachea because previous experience has shown loss of vascularity and motility with overzealous exposure.[2] The lower opening allowed placement of a right angle telescope. One end of a 5 cm length of flexible polyvinylchloride tubing was sutured to the margins of the lower tracheal opening in an airtight fashion for easy access to the lumen (Fig. 1). A Hopkins telescope with fiberoptic illumination was inserted through the tubing and used to visualize the upper trachea and its contents. Television monitoring with videotape recording was used for documentation.

The inside diameter of the trachea was measured at the time of initial exposure of the specimen and throughout the experiment, both at the level of the upper stoma and at the level of the tracheostomy tube cuff. The lower measurement was performed with a right angle caliper while observing the caliper through the telescope. Each measurement was performed five times and confirmed by two observers before insertion and after withdrawal of each tracheostomy tube.

Cuff-tracheal wall pressure was measured using a calibrated silicone envelope. Details of its construction and use can be found in a description by Numoto.[3] The use of this instrument to measure intratracheal CTP was documented in an earlier study by Galoob *et al.*[2] The envelope was secured to each tube and positioned against the antero-lateral tracheal wall. Care was taken to center the envelope on each cuff in order to record maximum pressures.

Pressure measurements were performed as follows: Each tracheostomy tube with its attached pressure measuring envelope was inserted through the upper tracheal stoma. Intracuff pressure was varied with an air-filled syringe and monitored with a pressure transducer. Cuff-tracheal wall pressure was monitored with a pressure transducer connected to the silicone envelope. Both ICP and CTP were recorded simultaneously. Initially all air was evacuated from the cuff with a syringe (-0 mm Hg). The cuff was then refilled and allowed to equilibrate with atmospheric pressure

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*Portex Division, Smiths Industries, Woburn, MA.

**Shiley Labs Inc, Santa Ana, CA.

†McGaw Labs, Irvine, CA.

††Extracorporeal Medical Specialists, King of Prussia, PA.

‡Medical Engineering Corp, Racine, WI.

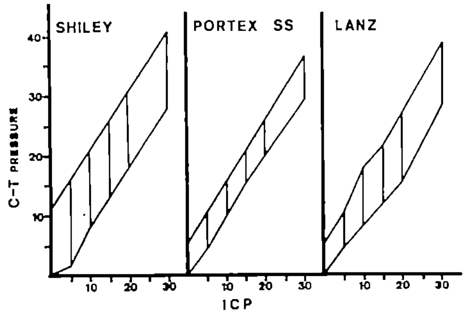

Fig. 2. Intracuff pressure (ICP) is plotted against cuff-to-tracheal wall pressure for each of three tubes: Shiley, Portex Soft Seal (SS) and Lanz. Variance of CTP obtained for each ICP is shown graphically. All pressures in mm Hg.

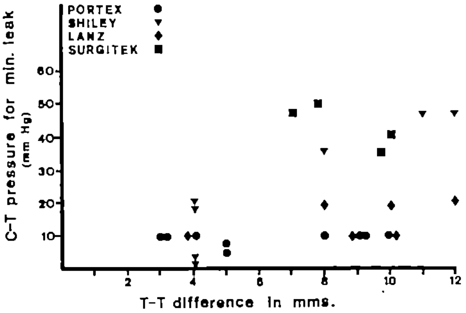

Fig. 3. The cuff-to-tracheal wall pressure necessary for minimal leak is plotted against the difference in diameter between tube and trachea (T-T difference).

(0 mm Hg). Pressure was increased in increments of 5 mm Hg up to a maximum of 60 mm Hg and the cuff allowed to deflate. The cycle of cuff inflation-deflation was repeated ten times for each tube. Each measurement of CTP was repeated five times to ensure accuracy.

Because of the different characteristics of the Bivona Fome-Cuf®, a slightly different procedure was used. This tube was inserted with the pressure measuring envelope attached. The cuff was alternately deflated and allowed to refill to atmospheric pressure. Cuff-to-tracheal wall pressure was measured at both extremes. The pressure-volume relationship for each Bivona tube was determined prior to placement in the animal as per the manufacturers instructions.* A pressure-volume curve was drawn from these data to predict CTP. Measured CTP were then compared with predicted CTP.

After the evaluation of pressures for each tube during spontaneous ventilation, the animal was placed on a respirator with 40% O_2 concentration. At least five minutes of ventilation were allowed before CTP were measured. Airway pressures of 30 and 40 cm H_2O were used. Each cuff was adjusted to minimal leak using a stethoscope tubing placed just above the tracheostomy tube cuff. Minimal leak was defined as the change in sound of airflow to a "squeaking" quality in the last one-third of the inspiratory cycle. A catheter placed inside the tracheostomy tube to the level of the tip allowed a graphic recording of respiratory cycle and absolute airway pressures.

Observations with videotape recordings were performed through the telescope before and after PPV. Movement of the tube tip and distal portion of the cuff could be seen. The behavior of the trachea during PPV was also observed. Minimal leak pressure determinations were performed with and without the pressure measuring envelope in place. Intracuff pressure alone was recorded after removal of the envelope and compared to the previous reading. This was done to document any changes in minimal leak which might be due to the presence of the pressure measuring envelope. Data obtained were subjected to statistical analysis. The average duration of each experiment was eight hours.

RESULTS

Relationship between ICP and CTP. Figure 2 shows the relationship between ICP and CTP for three types of tubes studied. Cuff-to-tracheal wall pressures obtained for the Portex Soft Seal cuff fell within a range of 5-7 mm Hg of intracuff pressure. The Lanz tube gave the next highest variance of 5-12 mm Hg. The Shiley cuffed tube shows the greatest variance, ranging from 10-15 mm Hg. There was no consistent relationship between ICP/CTP variance and tube-tracheal diameter (T-T difference) for the Portex, Shiley, or Lanz tubes. The Surgitek tube showed no consistent relationship between ICP and CTP. Since the cuff on the Bivona tube is self-expanding, it will be discussed separately.

Cuff-to-Tracheal Wall Pressure Necessary for Minimal Leak. Figure 3 illustrates the CTP necessary to obtain minimal leak using each tube and their relationship to T-T difference. Minimal leak pressures for both Portex and Lanz tubes consistently fell below 20 mm Hg regardless of T-T difference. Four of the Shiley tubes also lie in this range. However, substantially higher CTP were necessary in Shiley tubes with T-T differ-

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*Bivona Surgical Instrument Company: *The Rationale for the Fome-Cuf® Tracheal Tube,* Chicago, IL.

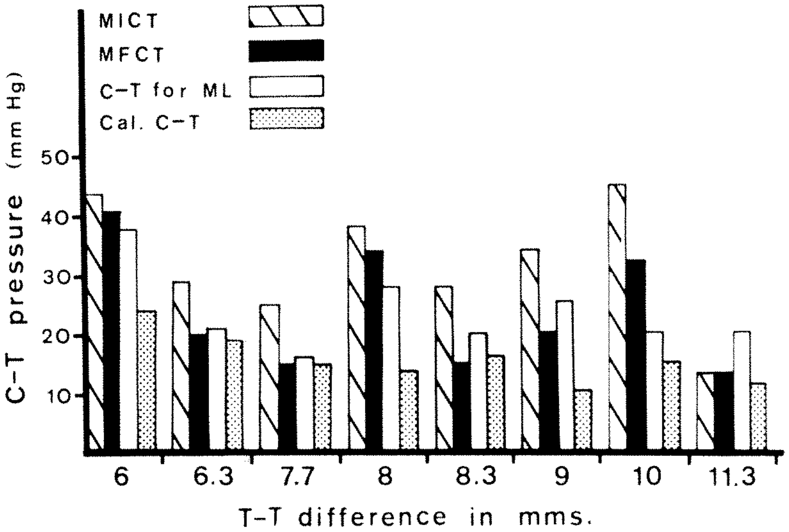

Fig. 4. Cuff-to-tracheal wall pressures for the Bivona Fome-Cuf® are illustrated. C-T pressures are plotted against the difference in diameter between tube and trachea (T-T difference). MICT - Mean initial cuff tracheal wall pressure; MFCT - Mean final cuff tracheal wall pressure; C-T for ML - Cuff tracheal wall pressure necessary to obtain minimal leak; Cal C-T - Calculated cuff tracheal wall pressure.

ences greater than 8 mm. All of the Surgitek tubes required greater than 30 mm Hg to obtain minimal leak.

Figure 4 shows the CTP obtained for the Bivona Fome-Cuf® tube at various T-T differences. The CTP necessary to obtain minimal leak are extremely variable for these tubes. Tubes are grouped according to T-T difference. Mean initial CTP (MICT) was greater than 25 mm Hg for all but one tube. In each preparation, the CTP decreased after a period of 30 minutes. In three tubes, however, the mean final CTP (MFCT) remained about 30 mm Hg. Additional air was necessary to produce minimal leak in all but three tubes when the animal was placed on the ventilator. This can be seen in those instances where the CTP for minimal leak (CT for ML) is greater than MFCT. The predicted CTP calculated from the prepared graph (Cal CT) was lower than the MFCT in every case. There appears to be no consistent relationship between the CTP obtained and T-T difference. A decrease in CTP was noted also after administration of intravenous pentobarbital and with PPV. These factors have been previously noted to cause tracheal dilation in animals[2] and will be discussed below.

Intratracheal Observations of Tracheal Dynamics. In the five animals in group I the tracheal diameter progressively increased with time as illustrated in Figure 5. This could have been due to the trauma of repeated insertion and withdrawal of tubes. Therefore only one brand of tracheostomy tube was evaluated in each animal in group II. Tracheal diameter was also noted to increase in this group but not as much as in group I. In all animals there was marked dilation above and below the cuff site in response to PPV. In group II, the trachea quickly regained its original size after discontinuing PPV. Intravenous pentobarbital also produced brief relaxation of the trachea with an average increase in tracheal diameter of 2 mm. This was reversible as the effect of the anesthesia lessened.

The intratracheal environment was observed continuously during the experiment. During spontaneous ventilation, the behavior of the trachea, the tube tip and tube cuff were easily observed and recorded on videotape. If a device with a diameter approximately two-thirds of the tracheal diameter was inserted, the

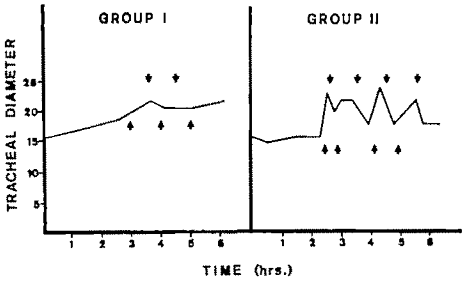

Fig. 5. Diameter of the trachea in millimeters is plotted against duration of the experiment in hours. For illustration each graph is representative of a single experimental preparation. GROUP I: Five different tube brands were evaluated in random sequence in each animal in this group. GROUP II: A single brand of tube was evaluated in each animal, but tubes of different sizes were used. ↑ - Start of PPV; ↓ - End of PPV.

trachea maintained a size that closely approximated the size of the indwelling tube. With insertion of a larger device the organ seemed to adjust partially. With extremes in tube size, however, it became apparent that the limits of dilation had been reached. Inflation of the cuff caused some dilation of the trachea below the cuff, and one could observe a small space between tube tip and tracheal wall. In those cases with minimal T-T difference the trachea appeared to grip the tube, preventing both torque transmission and encroachment of tube tip on the anterior wall.

The tracheal cartilages appeared to be under constant tension. Posteriorly, a ridge of mucosa could be seen as a constant feature in the unventilated animal. This midline ridge produced a groove on each side of the trachea. Suction catheters placed through the upper stoma could be diverted easily to either side if the appropriate groove was entered. In some animals the cartilage tips appeared to overlap, forming a solid but movable cartilaginous posterior wall.

Observations made during PPV revealed an entirely different picture. Within five minutes following the onset of PPV, the tracheal diameter increased 2 to 7 mm greater than the resting state, with a mean increase of 4.3 mm. The posterior fold of mucosa characteristic of the unventilated state, disappeared when the trachea dilated. It is under these conditions that the transmission of torque from tube connector to tube tip becomes an important consideration.

Transmission of Torque. The tracheal dilation that occurred during PPV increased the T-T difference and allowed much more tip movement than in the unventilated state. The flexibility of the Portex, Surgitek and Bivona tubes resulted in minimal observable torque transmission. Next, in increasing order of torque transmission, is the Lanz tube and finally the Shiley with nearly total transmission of torque to the anterior and lateral tracheal walls. The softer tubes transmit less torque in response to movement of the connecting end. The tip of the Lanz tube was consistently observed to be in contact with the posterior tracheal wall, causing indentation of the mucosa. Movement of the tip against the posterior wall during PPV was commonly seen and is of potential concern in the production of mucosal erosion. The Shiley tube, the most rigid of the tubes studied, transmits nearly 100% of the torque applied at the connecting end. Great care had to be taken in positioning the ventilator connections to prevent the tip of the Shiley tube from excoriating the anterior and lateral tracheal walls. The swivel at the connecting end did not appear to relieve this torque transmission. The higher ICP and CTP necessary to obtain minimal leak with this device and the increased T-T difference present during PPV, tended to force the tip of the instrument into the anterior tracheal mucosa even when care was taken in positioning the external connections. This occurred even with padding of the faceplate to simulate the human trachea-to-skin distance.

Tracheal Mucus. The viscosity of tracheal mucus appeared to play some role in cuff sealing. The surface of the cuff consistently was seen to "pop" away from the tracheal wall with deflation. This surface tension could account for some of the lower minimal leak pressures seen with the large surface area cuffs. This was less apparent during longer periods of PPV. The mucus also could

TABLE 1. CUFF RESIDUAL VOLUMES

	Outside Diameter of Tubes in mm							
	8.5		*10*		*11*		*12*	
	CV	*CD*	*CV*	*CD*	*CV*	*CD*	*CV*	*CD*
Portex	Not available		8.2	28	12	29	16	32
Lanz	3.8	20	Not available		14	30	16	30
Shiley	1.5	15	2.5	19	Not available		3.6	20
Bivona	16	30	20	31	25	32	26	33
Surgitek	0.4	9.5	0.4	10.7	0.4	12	0.4	13

CV - Cuff volume (cc); CD - Cuff diameter (mm).

be seen coating the inside of the tubes during the expiratory phase of ventilation.

Other Observations. During the course of the experiments certain other characteristics of individual tubes were noted:

1. Herniation of the large cuffs over the end of the tube could be produced with excessive intracuff volume and pressure. This always occurred at pressures in excess of that needed to produce a minimal leak. Overinflation and herniation were easier to accomplish in the Portex and Surgitek tubes than in the other tubes.

2. Migration of the inflated tracheostomy tube cuff occurred in all tubes except the Bivona. This consisted of the tube being funneled toward the more dilated stomal area. Excessive cuff inflation and pressures were commonly associated with this phenomenon; this did not occur during minimal leak conditions with any of the tubes.

3. A "pseudominimal leak syndrome" was discovered in several Portex tubes. A sudden increase in the pressure necessary to obtain minimal leak occurred on several occasions. Further examination revealed a small hole in the midportion of the cuff. To reproduce this phenomenon, tubes were first placed in the animal and minimal leak obtained at the usual low pressures. A pinhole was then made in the cuff causing an "apparent" minimal leak sound which occurred 20 or 30 mm Hg above the CTP originally required for minimal leak. Airway pressures were unchanged and the additional cuff pressure was found to be unnecessary for adequate ventilation. Leakage of air from the cuff occurred very slowly with an average decrease in pressure of 10 mm Hg during one hour. Perhaps the tracheal mucus intermittently sealed the pinhole, thus reducing the escape of intracuff air. Another possible explanation is the formation of an air bubble between the cuff and tracheal wall. The pathophysiology of this phenomenon is not yet clear, but its occurrence in animals supports the possibility of a similar unrecognized problem in humans.

Description of Cuffs. There have been numerous recent developments in the size and shape of tracheostomy tube cuffs. The design of each of the cuffs tested differs, and it is probable that before this work comes to print, even more changes will occur. For this reason it is important to describe the size and shape of each cuff, in order to make some comparison with past and future designs. Two characteristics are felt to be important: 1) cuff volume (CV) in cubic centimeters when fully expanded at atmospheric pressure, and 2) diameter of the cuff (CD) in millimeters when fully expanded at atmospheric pressure. These characteristics differ for each brand of tube and for different sizes of the same brand. This information is presented in Table 1.* At least three different sizes of each tube are presented with comparison between different brands of the same size. Several sizes of tubes were not available to us when the measurements were performed and this is stated in the table.

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*Cuff volume is measured for each cuff after removing all extracuff balloons and excessive tubing. There was no significant difference between atmospheric pressure and 1 cm H_2O intracuff pressure.

Description of Tubes. The controversy surrounding the use of a single lumen tube has continued for many years with advocates and proponents vehemently defending their viewpoint.[4] This study will not address the issue except to point out the theoretical arguments of both points of view. Use of the inner cannula was considered a necessity before the advent of widespread PPV. Crusting and obstruction of the lumen of the tube was not infrequent, and can be prevented by the simple technique of removing the inner cannula for cleaning without disturbing the airway. This method still has a great deal of merit for patients who are ambulatory and not receiving continuous ventilation. However, for critically ill patients on a ventilator, who are receiving continuous high humidity this has been shown not to be a problem.[5] The important variable here is the presentation of adequate humidity, for once this is discontinued, laminar crusting and obstruction will invariably begin. Of the tubes described in this study, only the Shiley has an inner cannula. The remainder are single lumen in construction. As observed previously, secretions tend to accumulate on the inner surface of the lumen and this must certainly be taken into account in the ultimate management and selection of the proper type of tube for a clinical situation.

DISCUSSION

The management of cuffed endotracheal and tracheostomy tubes is a perplexing clinical problem. Grillo and Cooper documented the role of cuffs in tracheal injury in dogs in 1969.[1] Since then there have been numerous approaches to prevent tracheal injury during PPV. The development of a "soft cuff" has been a central theme. Large volume, low pressure cuffs fashioned after the overstretched cuff of Geffen and Pontoppiden[6] have been shown to produce less injury than the lower volume "hard" cuffs previously in use.[7] Other approaches utilize self-expanding cuffs such as the Bivona Fome-Cuf®[8] and the parachute cuff developed by Abouav and Finley.[9]

The pressure exerted by cuffs has been measured in many ways. Early investigators placed a fluid-filled envelope between the cuff and the wall of the trachea or appropriate model. Adriani and Phillips[10] devised a rigid tracheal model with a transducer protruding into the lumen, and this method was used by Wu[11] to evaluate different types of cuffs *in vitro*. The present study utilizes an empty calibrated silicone envelope 1 mm in thickness. Thickness of the measuring instrument is an important consideration, because any change in the radius of the lumen theoretically affects the CTP. Tissue compatibility and a high degree of reliability make the silicone envelope an excellent device for measurement of *in vivo* surface pressure in animals and/or humans.

There are three components of CTP: 1) the force exerted by the cuff, 2) the force exerted against the cuff by the tracheal wall, and 3) the surface tension between the cuff and the tracheal wall. Tracheal mucus produces some surface tension and reduces the friction between cuff and mucosa. This may reduce local folds in the cuff surface, producing a more uniform application of pressure against the mucosa. The trachea was shown to be a dynamic and distensible organ. This characteristic may reduce the CTP as the tracheal wall moves away from the cuff. Conversely, pressure could be increased by a constricting tracheal wall. Pressure exerted by the cuff is a major component. The force exerted depends on the elasticity of the cuff material and the radius of the trachea. The actual force exerted on the tracheal wall is thus the sum of three vectors. These conditions are difficult to reproduce in a rigid, dry model, even when lubrication is applied to simulate intratracheal conditions.

Because the cuff and tip of a tracheostomy tube are not readily available for observation, indirect methods must be used. Prevention of injury from malfunction and misuse of these instruments can be achieved only by careful monitoring. The *in vivo* pressure measurements and simultaneous intratracheal observations described in this paper may offer considerable insight into the intelligent use of present day tracheostomy tubes. The very close relationship between ICP and CTP for the particular cuffs studied offers a reliable method of monitoring CTP at the bedside. Other individual tube characteristics suggest that all tracheostomy tubes may not be appropriate for every clinical situation. Based on the observations in this study, the following recommendations are presented as a guide for the selection of the proper tracheostomy tube for the proper clinical situation.

Shiley Tube. This device has several potential disadvantages for patients on prolonged PPV.

1. The tube wall is rigidly constructed and contains an inner cannula. There is a swivel plate to permit anterior-posterior excursion of the tube. The rigidity makes torque transmission a real problem and may lead to injury of the anterior wall by the tube tip. This may be accentuated in individuals with a thin neck and with increased T-T difference.

2. Cuff volume is less than 4 cc at atmospheric cuff pressure for all sizes (Table 1). Diameter of the cuff varies from 15-20 mm. This provides less than 6.5-9.0 mm for expansion of the cuff from any tube size. Expansion of the cuff beyond this diameter requires higher pressures and cancels the advantages of the floppy, overinflated "soft" cuff design. While low minimal leak pressures were obtained in most cases, the insertion of a tube with T-T difference of 8-9 mm may necessitate excessive cuff pressures for minimal leak. This is corroborated in Figure 3. In addition, excessive cuff pressures may force the tip of the tube anteriorly and potentiate the problems discussed in paragraph 1 above.

3. The Shiley tube is an excellent device for the ambulatory, unventilated patient where prevention of aspiration is desired with retention of an inner cannula. Caution should be used, however, in selecting the correct size tube. The tube should be changed to a larger size if excessive pressures are necessary for a seal. Symptoms of irritation from the tube, such as bleeding, excessive coughing, or pain should be followed up promptly with possible change to a different size or type of tube.

Portex Tube, Soft Seal Cuff. This single lumen PVC tube has a large volume-low compliance cuff and offers many advantages for patients on prolonged PPV.

1. The tube construction is flexible at room temperature. The material softens even more when heated, resulting in minimal transmission of torque.

2. The volume of the cuff measured at atmospheric pressure ranges between 8 to 16 cc of air for 10, 11 and 12 mm tubes. This large volume results in a potential increase of 18 to 20 mm in cuff diameter while still at atmospheric ICP. As a result of the large cuff size and wide range of cuff diameter without significant ICP very low CTP can be used to obtain minimal leak with a minimal relationship to T-T difference. Tube size is not critical for low minimal leak pressures as can be seen in Figure 3. C-T pressure may be monitored using ICP with an error of 5 to 7 mm Hg as noted in Figure 2. This ability to monitor pressures may serve as an early warning of malfunction in position or of cuff integrity if sudden increases in ICP become necessary to maintain minimal leak.

3. Malfunctions can occur, and this possibility should be an incentive for close monitoring. Some of the potential hazards are:

The tube may be milked into the stoma if not properly secured or if excessive pressures are used. An increase in the ICP necessary for minimal leak may indicate that this has occurred.

Overfilling of the cuff and excessive ICP may produce herniation of the cuff over the end of the tube with airway obstruction. This can be avoided with proper monitoring.

A pin hole in the cuff may produce the pseudominimal leak syndrome and is manifested by a sudden increase in ICP necessary for minimal leak. Loss of ICP may not be readily apparent in less than one hour.

Crusting of secretions with lamination

and obstruction of the tube may occur if proper humidification is not used.

Lanz Tube. This is a single lumen PVC tube with a large volume cuff and an overflow balloon built into the system. Its pertinent characteristics are as follows:

1. The Lanz tube is moderately flexible and only the Shiley tube transmits more torque.

2. The cuff volumes are similar to those found in the Portex cuff. The relationship of cuff diameter to tube diameter is also similar to the Portex cuff, with cuff diameters ranging from 20 mm to 30 mm as seen in Table 1.

3. As expected, the large cuff size results in a close correlation between ICP and CTP (Fig. 2), and tube size is not critical for minimal leak (Fig. 3). The extremely small tube sizes may not be applicable in the average adult.

4. A potential problem concerns the one-way check valve built into the system which allows air to flow easily into the cuff from the external safety balloon, but not in the reverse direction. The tracheal wall, as observed above, tends to accommodate any instruments placed within it. Thus, local extreme dilation and injury is possible. However, this phenomenon was not observed in this study.

Surgitek Tube. This tube is extremely flexible and its silicone construction makes it tissue compatible. The cuff has no residual volume and lies flat against the tube surface. This system offers the following characteristics.

1. Torque transmission is not a significant factor.

2. The cuff diameter at atmospheric pressure was never more than 1.0 mm greater than the tube diameter and cuff volume was less than .5 cc at atmospheric pressure for all tube sizes (Table 1).

3. Since a linear increase in ICP is required for any significant movement of cuff surface away from tube wall, there is no way of knowing at what point the cuff comes into contact with the trachea. Therefore, monitoring of ICP is not an accurate indicator of CTP.

4. C-T pressures necessary for minimal leak were excessive in all tubes tested.

5. In this study, we found that this device offers little advantage over the older low volume cuffs, in spite of its silicone construction and lower torque transmission.

Bivona Fome-Cuf® Tube. This is a single lumen tube of very flexible construction. The cuff system incorporates a contoured piece of foam sealed into a flexible silicone cuff. The pressure characteristics are alleged to be known for any given cuff volume and are provided in graph form by the manufacturer. The characteristics are:

1. Very little torque transmission.

2. The cuff diameter was the largest of all the tubes tested, however there was some discrepancy between CTP and calculated and measured ICP. The CTP can theoretically be obtained by measuring the residual volume of the cuff and using the graph supplied by the manufacturer. Pressures obtained by our method of direct measurement were significantly higher than the calculated pressures. This may be a manifestation of the direct method of measurement and may involve factors of surface tension present with the foam construction that were not present when measuring against an air filled balloon. Whatever the reason, it should be remembered that the same method of measurement was applied to all tubes included in the study.

3. There was evidence of active tracheal dilation in response to the force exerted by the foam cuff. This was manifested in several animals by an initial high pressure followed by a subsequent drop in CTP either spontaneously or in response to deepening of anesthesia (Fig. 4). The CTP remained high for several animals. The T-T difference may have been an important factor in these situations, however with the poor correlation between calculated and actual CTP, the ability to accurately detect this potential problem remains in doubt.

4. The change in tracheal diameter seen in the ventilated animal made it impossible to secure a minimal leak situation in most cases if the tubes were

placed during spontaneous ventilation. In these instances, air had to be added to the cuff to secure a seal.

5. The self-expanding nature of this cuff with the potential problems of cuff integrity and sealing pressure may make it unnecessarily complicated and unsuitable for routine use in ventilated patients.

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ADDENDUM

Since the original evaluation of the tubes and cuff systems discussed in this paper, there has been continual improvement and redevelopment by the respective manufacturers. Some brief comments concerning a recent (May 1977) reevaluation are appended.

Portex. There was much more difficulty in producing herniation in the newer tubes. In all cuffs tested, rupture of the cuff occurred before herniation was produced.

Shiley. This tube is now being produced with a venting system and a much larger volume cuff. The venting system appears to prevent excessive cuff pressures during cuff filling with the syringe in place. However, it does not compensate for increased cuff pressures that occur when the system is closed. The larger cuff does not successfully buffer torque transmission to the tube tip at lower intracuff pressures.

Lanz. The current Lanz system demonstrates consistent backflow from cuff to overflow balloon with the valve in closed position, producing equilibration between the two. Flow back with the valve closed is much slower than with the valve open. Equilibration of cuff and overflow balloon pressures takes approximately ten minutes. Contrary to the previous evaluation, this system does compensate for excessive cuff pressures. However, there are several characteristics that the user should be aware of: 1) Use of the system without pressure monitoring may result in cuff pressures higher than that necessary to achieve minimal leak. This may occur as the cuff pressure becomes a direct function of the pressure in the overflow balloon. 2) There is a theoretical possibility of intermittent increased cuff pressures because of the slower action of the flow back system. If one does not wish to monitor the pressure in this system, the action of the overflow balloon will prevent inadvertent overfilling of the cuff. However, pressures slightly higher than necessary may result. The significance of this has not been determined.

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RESPONSE OF FIRST ORDER VESTIBULAR NEURONS TO LIDOCAINE HYDROCHLORIDE

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SUMMARY — Changes in behavior and electrical activity of primary vestibular neurons were observed following injection of lidocaine hydrochloride into the middle ear of cats. After injection the cats exhibited head and ocular nystagmus, head and neck deviation and pupillary changes. Mean preinjection resting discharge rate for first order vestibular neurons was 46.0 spikes/sec. Two hours after lidocaine application the resting rate decreased to a mean of 22.2 spikes/sec and then recovered to 43.0 spikes/sec four hours, and 47.7 spikes/sec six hours after the experimental treatment. The incremental sensitivity (increased rate of firing) of horizontal canal neurons to constant angular acceleration for the control period was 2.0 extra spikes/sec/deg/sec^2; two hours after the application, 70% of the recorded neurons were unresponsive to angular acceleration or tilt. The sensitivity after four hours was 1.0 spikes/sec/deg/sec^2 and 2.1 spikes/sec/deg/sec^2 at six hours. The distinct depression of sensitivity by lidocaine at four hours compared to normal mean resting rate at this time suggests these functions may be governed by two modes of action in the receptor or first order afferents.

Lidocaine hydrochloride is frequently used as a local anesthetic for middle ear surgery. Recently it has been shown that a 4% lidocaine application to the middle ear results in brief reversible depression of labyrinthine function in humans.[1] This depression effect is useful in evaluation of the extent and nature of inner ear lesions.[2,3]

There are numerous studies which have been directed toward the effect of local anesthetics upon labyrinthine function, such as cocaine,[4] procaine hydrochloride,[5,6] tetracaine hydrochloride,[7] and lidocaine hydrochloride.[8-10] However, most of these investigations were concerned with the effect of chemical agents on cochlear functions, except for Jenkins *et al*,[9] who reported on behavioral changes such as head and ocular nystagmus in the cat after a middle ear application of lidocaine.

This report describes the temporarily reduced depression of primary vestibular neurons, as evidenced by postural changes and alterations in the neuronal discharge patterns resulting from the middle ear application of lidocaine in the cat.

METHODS AND MATERIALS

Twenty cats weighing 2.0 to 4.2 kg were used in this study. Five of these cats were used for behavioral observation in addition to the recording of electrical activity from primary neurons. The cats were lightly anesthetized with ether and 4% lidocaine was injected into the middle ear cavity through the tympanic membrane. Ether anesthesia was discontinued prior to a lidocaine application. After injection the animals were freed and allowed to roam in order to observe behavioral changes.

Twenty cats were used to record the electrical activity of primary vestibular afferent neurons. The animals received pentobarbital sodium (40 mg/kg) intraperitoneally and following a tracheotomy were placed in a stereotaxic frame. To expose the primary neurons for recording, a right parieto-occipital craniotomy was performed and portions of the paraflocculus and the flocculus were aspirated. The roof of the internal auditory meatus was removed under an operating microscope with a small cutting burr and the vestibular nerve was exposed. By this method both the superior

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(Editor's note) This paper is basic research, but contains clinical significance for otologic surgeons. If and when lidocaine HCl diffuses into the inner ear, causing vestibular symptoms through paralysis of the first order neurons, these changes are completely reversible.

and inferior division of the vestibular nerve could be visualized.[11-12] During the experiment the exposed nerve was covered with warm Ringer's solution. Following the nerve exposure, the animal was moved in the stereotaxic frame to a nearby gimbal-turntable apparatus.[12] The basic stimulus head position was with the nose of the cat angled 22° below stereotaxic horizontal and rolled 6° right ear down.[12] The animals were then given gallamine triethiodide (10 mg/kg) and were artificially respired for the remainder of the experiment. The body temperature of the animals was maintained at 37-38 C by an infrared lamp.

Extracellular activity from single primary afferent neurons was recorded in the area of Scarpa's ganglion with glass microelectrodes filled with 2M NaCl (DC resistance 2-5 M ohm). The electrode was coupled to a cathode follower and amplifier both on the turntable. The spike activity was led through slip rings to a cathode ray oscilloscope and a comparator circuit which allowed conversion of spike firing frequency to a DC voltage. The latter was fed into a Brush strip chart recorder.

Recording was limited to neurons located in the superior division of the vestibular nerve. Electrode placement was done visually under an operating microscope, and the recording depth was limited to a maximum of 700μ below the point where the electrode first touched the nerve. Three types of neurons were identified: cells that responded to natural stimulation of the 1) horizontal or 2) anterior semicircular canals, and 3) otolith neurons responding to change in static head position. The technique for functional identification of anterior or horizontal canal neurons is covered in Estes *et al.*[12]

Prior to the lidocaine application, resting rates and stimulus-response characteristics were recorded. A trapezoidal acceleration profile described by Blanks *et al*[13] was used. This consisted of constant angular acceleration of 2 to 19 deg/sec^2, followed by a period of constant velocity of about 200 deg/sec for about 40 seconds, and constant deceleration of about 4 deg/sec^2 to zero velocity. These trapezoidal accelerations were carried out only on horizontal semicircular canal neurons. Under optimum conditions units were held 30 minutes. Following the lidocaine injection, resting rate frequency and sensitivity to acceleration were determined at two-hour intervals for six hours.

Two techniques of lidocaine application were used. In one procedure the lidocaine was injected through a hollow ear-bar into the middle ear. In the second procedure, a small opening was made into the tympanic bulla via a lateral approach and the lidocaine injected through this. Both methods proved equally effective.

RESULTS

BEHAVIORAL OBSERVATION

The initial signs of application of lidocaine to the middle ear were paralysis of the ipsilateral nictitating membrane so that it partly covered the opened eye and pupillary constriction. This was followed by facial weakness on the anesthetized side (absence of spontaneous facial movement and blinking reflex). The cats also showed head and ocular nystagmus toward the contralateral side with horizontal-rotatory components. Of the five tested, three cats showed spontaneous nystagmus within five minutes after an application and one exhibited nystagmus in 20 minutes. The freely moving cats showed severe staggering and head deviation toward the anesthetized side. In five to six hours following an injection, these signs disappeared and cats behaved normally. One cat did not show any signs of labyrinthine paralysis. At the conclusion of the experimental session the middle ear was observed under the operating microscope and showed evidence of previous infection, manifested by thickening of middle ear mucosa and scar tissue covering the round window membrane.

OBSERVATION OF PRIMARY VESTIBULAR AFFERENT NEURONS

Before a lidocaine application, 159 units were sampled as controls. Eighty-four responded to natural horizontal canal stimulation, 38 to anterior canal stimulation, 33 to otolith stimulation and 4 showed no response to natural stimulation. Nerves were considered to be nonresponding only when they occurred in a field of responding neurons, thus eliminating from consideration those units which were either not responsive because of malposition of the electrode or poor condition of the animals. At rest, all units fired tonically and most fired regularly. While "regularity" was not evaluated in the present study, the units were qualitatively comparable in this regard to those we have previously studied.[12] The resting discharge rate for the 159 units ranged from 1 to 94 spikes/sec (mean 46.0 ± 23.1 standard deviation). The mean for the horizontal canal neurons was 47.2, for anterior canal units 50.7 and for the otolith units 37.6. Seventy-one other vestibular neurons were used as con-

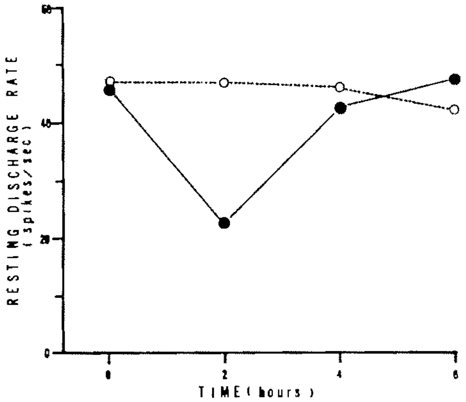

Fig. 1. Change in resting rate before and after lidocaine application. Filled circle indicates the means of the resting rates. Open circle represents the mean value of the control neurons at each period.

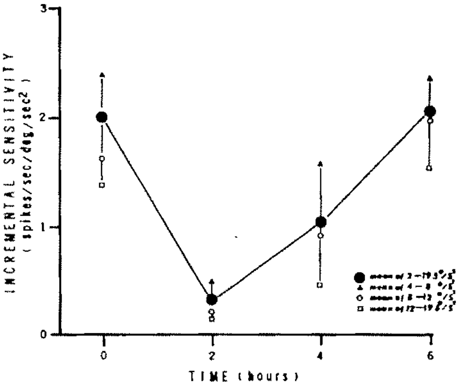

Fig. 2. Change in incremental sensitivity to constant angular acceleration before and after lidocaine application. Filled circles indicate the means of sensitivity at accelerations from 2 to 19.5 deg/sec². Open triangles, open circles and open squares indicate the sensitivity recorded at ranges of 4-8, 8-12 and 12-19.5 deg/sec².

trols to determine changes, if any, in resting rate with time alone following surgical exposure of the VIII nerve (*i.e.*, no lidocaine was put in middle ear). The mean resting rate shortly after exposure was 47.4 spikes/sec (n = 18). At two hours it was 47.2 (n = 16), at four hours it was 46.3 (n = 15) and at six hours it was 42.2 (n = 22). These differences are not significant. (See dotted line in Fig. 1.)

In response to prolonged angular acceleration, some units were characterized as adapting because their discharge rate reached a maximum and then decreased somewhat even as acceleration continued. These units showed an undershoot at the end of acceleration. Other neurons, considered as nonadapting, had their firing rate increase to a maximum during acceleration and then maintained that value to the end of acceleration. If the acceleration was brief because of either a high value of acceleration (8-16°/sec²) or a low terminal velocity (150-160°/sec), an adapting characteristic could not be determined. Of 37 horizontal canal units examined before lidocaine instillation, 10 were adapting, 17 were nonadapting and 10 could not be classified.

Sensitivity, as the term is used in this experiment, refers to the comparison of the unitary response at a given moment in time to the applied stimulus, angular acceleration. It is expressed as the number of extra spikes/sec/degree/sec². Incremental sensitivity, based on the increased firing rate during acceleration (as opposed to other closely similar values obtained during deceleration), is calculated as shown in the fourth figure of Blanks *et al.*[13] Decremental sensitivity is a measure of the reduced firing rate during deceleration.[13]

Thirty-seven horizontal canal neurons tested were stimulated with a range of acceleration from 2 to 19.5 deg/sec.² For those 37 units the mean incremental sensitivity at accelerations from 4 to 8 deg/sec² was 2.4 spikes/sec/deg/sec.² For 8 to 12 deg/sec² the increase was 1.6 spikes/sec/deg/sec² and for accelerations ranging from 12 to 19.5 deg/sec² the increase was 1.4 spikes/sec/deg/sec². The sensitivity over the whole range of acceleration value (2 to 19.5 deg/sec²) was 2.0 spikes/sec/deg/sec² (Fig. 2). Mean decremental sensitivity of 23 horizontal canal neurons during mean deceleration of 4°/sec² was 2.3 spikes/sec/deg/sec².

Initial Depression After Lidocaine Administration. Continuous records of 5 neurons were made during the lidocaine injection and the initial depression in

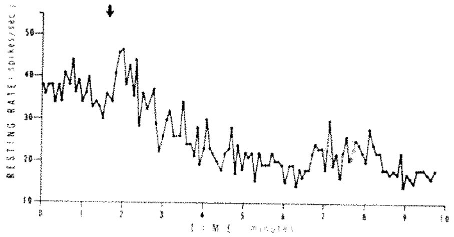

Fig. 3. Change in resting rate following a lidocaine application. The resting discharge rate of a single horizontal canal neuron is depressed after a lidocaine application, indicated by a downward arrow. Each point represents the resting rate (spikes/sec) at every five seconds.

resting rate which followed. Three cells showed decrease in discharge frequency within two to three minutes (Fig. 3). One showed no decrease until 11 minutes after the injection and the other exhibited a delay of 30 minutes. The maximal depression of resting rate compared to control values ranged from 39 to 93% during the period of observation (8 to 36 minutes).

Unit Observation After Two Hours. Forty-three units were sampled during the period of two to 2½ hours after a lidocaine application. Thirty out of 43 units (70%) did not respond to angular acceleration or static change in position. The percentage of nonresponding units varied from cat to cat, ranging from around 40 to 90%. Of the 13 responding units, 8 were horizontal canal, 2 were anterior canal and 3 were otolith neurons. The mean resting rate for the 43 units was 22.2 spikes/sec. This rate was significantly lower than the control value ($P < 0.001$). The resting rate of the 30 nonresponding units was especially low (8.2 spikes/sec) (Fig. 1 and 4B). Sensitivity to angular acceleration at two hours was low (mean 1.2 extra spikes/sec/deg/sec^2) in the five horizontal canal neurons which responded to natural stimulation. Based on percentages of identified neurons during the control period, we estimate about 50%, or 15/30, of the nonresponding units were horizontal canal units. Their sensitivity would, of course, be zero. To a rough approximation, we may say the mean sensitivity of all the horizontal canal neurons was around 0.3 spikes/sec/deg/sec^2 (Fig. 2). Approximate mean decremental sensitivity calculated same method as incremental sensitivity was 0.4 spikes/sec/deg/sec^2.

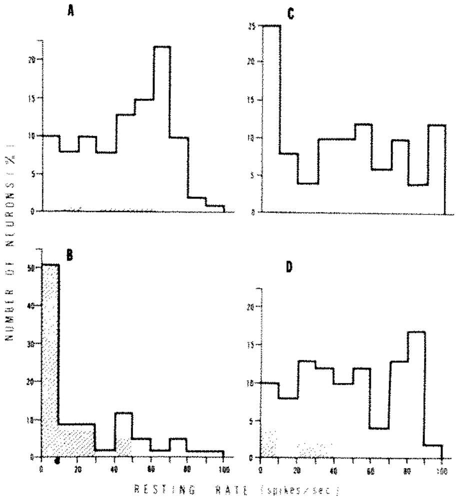

Fig. 4. Population distribution of the resting discharge rates for all the cells. A) Normal resting rate prior to injection. B) Two hours. C) Four hours. D) Six hours after lidocaine application. Open area indicates neurons which responded to natural stimulation (horizontal canal, anterior canal and otolith neurons). Shaded area represents cells which were unresponsive to angular acceleration and tilt.

Unit Observation After Four Hours. Fifty-one units were observed during the period of four to 4½ hours after an application. Forty-five out of 51 neurons responded to angular acceleration or otolithic stimulation (horizontal 21, anterior 10, otolith 14). The mean resting rate was 43.0 spikes/sec (Fig. 1) which was not significantly different from the resting mean of control (46.0 spikes/sec). Figure 4A and C shows resting rate histograms of unitary activity recorded during the preinjection and four hours postinjection periods. Even though they seem to show different distribution characteristics, statistically these sample distributions appear to be from the same population according to the Kolnogorov-Smirnov test. During this period, acceleration profiles to determine sensitivity ranging from 3.3 to 18.5 deg/sec^2 were employed on 12 horizontal canal neurons. The average incremental sensitivity for all the units was 1.0 spikes/sec/deg/sec^2 with S.D. of 0.8 (Fig. 2). This value was significantly lower than the control ($P < 0.001$). The sensitivity at the acceleration range of 4 to 8°/sec^2 was 1.6, for the range of 8 to 12°/sec^2 was 0.9 and with acceleration from 12 to 19.5°/sec^2 was 0.5. Mean decremental sensitivity of 9 neurons at deceleration level of 4°/sec^2 was 1.8 spikes/sec/deg/sec^2. This value was significantly lower than the control (2.3).

Unit Observation After Six Hours. After a period of six to 6½ hours, 52 units were sampled. Forty-eight out of 52 units responded to acceleration or to tilt (horizontal 23, anterior 14, otolith 11). The mean resting rate was 47.7 spikes/sec and statistically no significant difference was obtained between this and the control resting rate. The firing distribution of resting rates (Fig. 4D) was close to control statistically (Fig. 4A). Sensitivity measures were taken on 15 of the 23 horizontal canal units. Acceleration level ranged from 3.9 to 17.7 deg/sec^2. The mean incremental sensitivity was 2.1 spikes/sec/deg/sec^2 with S.D. of 1.4 (Fig. 2). Statistical analysis revealed no significant difference between this and the control value. The sensitivity at the level of 4 to 8, 8 to 12 and 12 to 19.5°/sec^2 were respectively 2.4, 2.0 and 1.5 spikes/sec/deg/sec^2. Mean decremental sensitivity of eight horizontal canal neurons at deceleration level of 4°/sec^2 was 2.4 spikes/sec/deg/sec^2.

DISCUSSION

BEHAVIORAL OBSERVATION

Behavioral changes after a lidocaine application have been studied by Jenkins *et al*[9] in cats and Yagi and Suzuki[3] in humans. Pupillary changes and facial weakness were not reported in these previous studies. Barlow and Root studied the ocular sympathetic pathway by anatomical and physiological methods in the cat. They reported that the postganglionic ocular sympathetic nerves left the superior cervical ganglion, passed between the tympanic plates of the auditory bulla and the inferior surface of the petrous bone, and some of the fibers appeared in the chamber of the middle ear. Electrical stimulation of the numerous fibers which crossed the promontory caused a dilatation of the pupil and a constriction of the nictitating membrane, and the destruction of the fibers caused miosis and protrusion of the nictitating membrane. Barlow and Root observed no ocular change after a labyrinthectomy which did not destroy the sympathetic fibers crossing the promontory. It is reasonable to ascribe the ocular changes observed after lidocaine injection in this study to depression of action of the sympathetic nerves crossing the middle ear cavities. Facial weakness appears to be due to paralysis of the middle ear portion of the facial nerve. The facial canal frequently has bony dehiscences in the cat as well as humans. In cats, T. Hoshino observed four temporal bones from two cats and found bony dehiscences in each case.* We examined four temporal bones from four cats and also found wide bony dehiscences in all cases. Baxter[15] found bony dehiscences from 55% of the examined human temporal bones. Lidocaine probably invades the facial nerve through such openings. The facial weakness in humans has also been observed during middle ear surgery under lidocaine anesthesia.**

Behavioral changes persisted for five to six hours following a lidocaine application and then entirely cleared. From this it can be concluded that the local anesthetic effect is both temporary and reversible. The duration of the anesthesia was similar to human cases, differing only in onset latency. In humans the effect begins in 20-40 minutes[3] as opposed to cats, where the time of onset was 5 to 20 minutes. Hughes and Yagi[10] noted in cats that perfusion of 4% lidocaine into the bulla and middle ear space without contact to round window membrane failed to cause depression of cochlear function. We feel this evidence confirms the round window membrane as the point of infiltration for the lidocaine.

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*Unpublished data.

**Goodhill V: Personal communication.

Regarding recovery of function following a lidocaine application to the middle ear, Rham *et al*[8] stated that 4% lidocaine without epinephrine caused permanent damage to cochlear functions in the cat. However, Hughes and Yagi[10] and Yagi and Suzuki[3] observed complete recovery of microphonics and action potentials in the cat and vestibular functions in humans. The present study provides supportive evidence that a lidocaine anesthetic effect upon the inner ear is both temporary and reversible.

VESTIBULAR PRIMARY AFFERENT OBSERVATION

The mean resting discharge rate in the control study was 46 spikes/sec (range of 1-94 spikes/sec). This mean value is somewhat higher than that observed by Estes *et al,*[12] who found a mean of 36 spikes/sec (range of 0.54-114.0 spikes/sec). Other studies in the cat include that of Rupert *et al*[16] who reported 3 to 125 spikes/sec and Walsh *et al*[17] with values from less than 10 to 110. Unfortunately, those works did not report the mean rates. Results from the present study showed that two hours after the experimental treatment the average resting rate frequency decreased to a mean value of 22.2 spikes/sec, recovering to 43.0 spikes/sec after four hours and to a mean value of 47.7 spikes/sec after six hours.

Recently, sensitivity to constant angular acceleration of the primary vestibular afferent neurons was studied by Blanks *et al.*[13] They found the mean incremental sensitivity of horizontal canal neurons at acceleration range of 4 to 6°/sec^2 was 1.7 spikes/sec/deg/sec^2. In the present study, the mean incremental sensitivity for the control period was 2.0 spikes/sec/deg/sec^2 for the acceleration ranges from 2 to 19.5°/sec^2. Two hours after the lidocaine injection 70% of the recorded units showed no response to natural stimulation. The unit sensitivity after four hours was 1.0 spikes/sec/deg/sec^2 and 2.1 spikes/sec/deg/sec^2 six hours after the application of lidocaine.

The response characteristics of the neurons to constant angular acceleration has been classified into three types: nonadapting (NA), adapting (AD) and reverse adapting (RA).[13] In the present experiment we found only the first two types, plus others we could not classify. Of those cells recorded from during the control period, 25 of the 38 neurons were put into one of these three categories: NA/17, AD/8, nonclassifiable/13. There was no significant difference in the NA/AD cell types sampled four and six hours after a lidocaine application (NA/6, AD/3, nonclassifiable/3 and at six hours NA/8, AD/4, nonclassifiable/3). While the sample size is small, it appears lidocaine does not alter the adapting/nonadapting properties of neurons.

A spontaneous resting discharge is almost the rule in recording from myelinated axons from cochlear,[18] vestibular[12,19,20] and lateral line organs,[21] with the resting rate apparently becoming faster and more regular in higher species. Each myelinated axon divides into several unmyelinated branches, which in turn make synaptic contact with a number of receptor hair cells. The precise steps by which the graded receptor potentials in each of the several receptors result in action potentials in the myelinated nerve is unknown. However, it was likely the lidocaine inhibition in the middle ear depressed the resting rate by action both on the receptor and on the nerve. The former possibility is supported by lidocaine's prompt and prolonged depression of the amplitude of cochlear microphonics,[10] which depend on normal cochlear hair cell function.[22] It seems likely vestibular hair cell function is similarly affected. It also seems reasonable to invoke an anesthetic effect of lidocaine on the vestibular nerve on two grounds: 1) the depression of cochlear nerve action potential is prolonged, and the maximal effect is much more prolonged than is the depression of the cochlear microphonics[10] and 2) other nerves in or near the middle ear, the facial and sympathetic nerves, are significantly depressed in the present experiment.

The mean sensitivity of response of vestibular neurons to angular acceleration is reduced for a longer period of time than is the mean resting rate. Wedenski described a phenomenon in peripheral nerves in which the partially narcotized nerve failed to respond with a very high rate of stimulation, while still responsive to slowly repeated stimuli (Wedenski inhibition).[23] If our findings were to be explained in light of this phenomenon, it would seemingly offer an explanation of the different recovery rates of resting frequency and incremental sensitivity as mentioned above. The logic of such an explanation would be as follows. The recorded activity rate found in the resting state could pass the partially blocked nerve because of its low frequency, while higher frequency impulses, such as those found in a response to acceleration, would fail to pass the partially narcotized nerve. However, in this study, decremental sensitivity, a measure of decreased firing rate during deceleration, is also depressed. If Wedenski inhibition allows lower frequency impulses to pass, then decremental sensitivity should not be depressed. Therefore, Wedenski inhibition is an unlikely explanation of our result. Matthews and Rushworth[24] examined the effect of procaine on the stretch reflex and found a selective action of local anesthetics to be on the gamma-motoneurons and alpha-motoneurons. Yet this effect, presumably based on differences in thickness of myelin sheath and in axonal diameter, is difficult to relate to the present experiment. At present we cannot offer a reasonable explanation for the difference in recovery rate of resting discharge and of sensitivity to angular acceleration after lidocaine.

Concerning the consistency of the lidocaine effect, the percentage of cells showing the depression effect of lidocaine was found to vary from animal to animal. In some cats about 90% of the units tested two hours after a lidocaine application did not respond to natural stimulation, while in other animals during the same period 40% of the units tested showed no response to natural stimulation. We might speculate that this inconsistency may be due to variability in the round window membrane permeability to lidocaine.

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EFFECTS OF COMBINATIONS OF SODIUM SALICYLATE AND NOISE ON THE AUDITORY THRESHOLD

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SUMMARY — Thirty-nine monaural chinchillas were used to study the interaction between sodium salicylate and various TTS-producing noise paradigms. Five animals were included in each of the following three groups: 1) sodium salicylate (400 mg/kg) plus 2-4 kHz, 95 dB SPL noise band for one hour; 2) sodium salicylate (400 mg/kg) plus 4 kHz CF octave band noise at 80 dB SPL for 96 hours; and 3) sodium salicylate (400 mg/kg) plus 50 impulses having 50 μsec A-duration and 158 dB peak SPL, presented at one per minute. The remaining 24 animals served as various controls in groups exposed to sodium salicylate or the noise paradigm alone. Thresholds were estimated before, during, and after exposure using the AER technique and cochleagrams were mapped for each cochlea 30 days after exposure. When sodium salicylate was combined with the various noise conditions, the maximum TTS values obtained from the combination studies were comparable to those obtained from the single agent producing the greatest TTS at a particular frequency. No consistent alteration in either magnitude or time course of posttreatment threshold shift was found following the combination treatments as compared to the individual agents alone. Hazard to the auditory system resulting from a combination of sodium salicylate and noise was concluded to be no greater than the hazard presented by either agent alone. This result is also substantiated in the histological results.

It is well-known that both intense sounds and certain drugs present a hazard to the auditory system. Recently, experiments have established a potentiating effect of both ototoxic drugs and noise, *e.g.*, noise and noise, noise and drugs, drugs and drugs.

Noise and Noise. Combinations of impulse and continuous noise have produced dichotomous results. Low levels (90-110 dB for 15 minutes and 124-127 dB impulses) in combination produced lower levels of TTS than exposure to either noise alone. This reduction in temporary threshold shift (TTS) was assumed to be mediated by the acoustic reflex.[1-3] Higher level combinations (95 dB SPL 2-4 kHz and 158 db p.e. SPL impulses) produced massive losses of the sensory cells and large permanent threshold shifts, while each noise alone produced no lasting audiological or histological changes.[4]

Drug-Drug Interaction. A potentiating interaction between the aminoglycoside antibiotics as well as between other ototoxic agents (quinine, ethacrynic acid, salicylates, *etc*) has been demonstrated. Frost *et al*[5] presented evidence of kanamycin therapy predisposing a patient to the ototoxic effects of a relatively low dosage (1 gm/day/30 days) of streptomycin.

West *et al*[6] used the AC cochlear potential as an indication of the status of the cochlea when guinea pigs were given kanamycin, ethacrynic acid, and the two drugs in combination. When the drugs were administered in combination, the cochlear potentials were depressed in a manner analogous to ethacrynic acid acting alone. However, approximately two hours after administration of the two drugs, the CM was further depressed to a level much

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greater than would have been caused solely by the ethacrynic acid.

Prazma *et al*,[7] using guinea pigs and relying upon electrophysiological measures (AP, CM, EP), also showed a potentiation of ethacrynic acid and kanamycin.

Drugs and Noise. High level industrial and recreational noise environments, coupled with the increased outpatient use of various antibiotics, has stimulated interest in the effects of combinations of noise and drugs. Dayal *et el*[8] studied the effect of incubator noise (68-72 dB) on kanamycin-treated guinea pigs. Using the surface preparation to study the status of the cochlear hair cells, they showed a loss of nearly twice the number of apical hair cells when 15 mg/kg was administered with the noise background and four times the loss when the dosage was increased to 50 mg/kg.

Neomycin with continuous noise and kanamycin with impulse noise have also been shown to produce an interaction. One interesting and unexpected result of Darrouzet and Sabrinho[9] showed that noise followed by kanamycin treatment produced more serious cochlear damage than when the reverse order of ototraumatic agents was presented.

The salicylates are an interesting class of ototoxic agents because they produce a hearing loss that is strictly temporary. In fact, except for a few isolated cases,[10] the temporary nature of the salicylate-induced hearing loss seems to be preserved even when maximal doses of the drug are administered repeatedly over a long period of time.[11,12]

The nature of salicylate-induced hearing loss has been investigated in animals and man. In the monkey, TTS following intramuscular injection of sodium salicylate reaches a peak of from 22 dB (250 mg/kg) to 34 dB (500 mg/kg) at 4 kHz one to six hours postinjection. In man, the TTS during a state of salicylate intoxication following aspirin ingestion may be as much as 40 dB.[12] In both primate species, recovery is typically complete in 24-72 hours. The hearing loss appears to be dependent on salicylate blood levels and is bilaterally symmetrical.[11,13] Although the dependency of magnitude of TTS on salicylate blood levels has been reported to be consistent by several investigators,[13,14] considerable variability in human subjects has also been reported.[15] The loss of sensitivity, for the most part, has been found to be uniform throughout the frequencies tested, *i.e.*, a "flat" audiometric configuration.[11,14] This finding has been disputed by McCabe and Dey[12] who reported a greater loss in the higher frequencies (4 kHz and 6 kHz) in some patients. At present, there is no consensus as to the frequency configuration of hearing loss produced by salicylate ingestion.

Anatomical Correlates of Salicylate Ototoxicity. The most consistently observed anatomical alterations in experimental animals following salicylate ingestion involve the stria vascularis. Covell[16] and Myers and Bernstein[11] reported changes in the shape of the marginal cells of the stria vascularis and the mitochondria of these cells in guinea pigs following repeated sodium salicylate doses of 200 mg/kg, and in monkeys following a single 500-600 mg/kg dose. Swelling of the endothelial cells in the capillaries of the stria vascularis in guinea pigs treated with a single .5 ml dose of sodium salicylate has been reported by Folbe-Hansen.[17] Hawkins[18] reported absence of erythrocytes in the vessels of stria vascularis in guinea pigs following administration of a single large dose of sodium salicylate.

The salicylates present an interesting problem; unlike other known ototoxic drugs, their effect is presumably temporary. Most of the other ototoxic drugs have been shown to enhance the autotraumatic effect of noise. The question to be explored in this paper is whether sodium salicylates interact with noise exposures involving relatively high-level, short duration noise, lower-level, long-duration noise, and impulse noise. The strategy was to combine sodium salicylate with classes of noise that are representative of the range of acoustic

TABLE 1. SALICYLATE BLOOD LEVELS

Animal	*Wgt/gm*	*Date*	*Sal. Dose mg/kg*	*Sal. Blood mg/100cc*	*Hrs Postinjection*
101	440	9/6/73	400	51.	2.75
85	470	9/6/73	400	78.	2.66
13	395	9/7/73	400	70.	2.90

$\bar{X}$ 400 mg/kg — 65.3 mg/100cc
Sal. - Salicylate.

environments that might be encountered in realistic situations.

METHODS AND MATERIALS

Subjects. Thirty-nine chinchillas, including controls, were used as subjects. Each animal was anesthetized with sodium pentobarbital (50 mg/kg, I.P.) and rendered monaural by means of surgical destruction of the left cochlea. While anesthetized, a chronic electrode was placed on the dura, over the region of the inferior colliculus, and a reference electrode was inserted into the nasal cavity. The electrodes were attached to a two-pronged transistor plug which was fastened to the skull with cranioplastic cement. The animals were allowed to recover for 3-7 days.

Audiometric Testing. Following the recovery period, auditory evoked response (AER) audiograms were obtained from each animal.[19] Thresholds were obtained at test frequencies of 0.5, 1, 2, 4 and 8 kHz. The test signal was a 22 msec tone burst with a 5 msec rise-fall time. Threshold was considered to be the halfway point between the lowest intensity eliciting a definite N_1-P_1 response and the highest intensity producing no response. AER tests were performed in a calibrated acoustic booth (IAC AC3). At least two pretreatment thresholds were obtained at each of the five test frequencies; preexposure threshold was taken as the mean of these two or more values.

Cochlear Histology. All chinchillas in this study were sacrificed approximately 32 days after their exposure to one of the paradigms described below. The bulla was removed after decapitation and the cochlea immediately perfused with cold, buffered OsO_4. After fixation, the cochleas were rinsed, dehydrated and dissected. The entire organ of Corti was removed and mounted for the surface preparation. The tissue was studied at 400X using a Zeiss differential interference contrast microscope and cochleagrams were prepared.

Noise Sources. The continuous noise system consisted of a standard laboratory audio system (*i.e.*, noise generator, filter, amplifier, speaker). The animals were exposed in a semireverberant environment. The impulse noise was generated using a high-energy (127 J) capacitator discharge (25 KVDC) across a .32 cm air gap. The impulse produced had a 50 μsec positive over-pressure duration. For the impulse noise exposure, the animals were restrained and exposed at a normal angle of incidence in an anechoic surrounding.

Salicylate Treatment. Three chinchillas were injected with 400 mg/kg of sodium salicylate intramuscularly and salicylate blood levels were determined between two to three hours postinjection. The sodium salicylate was kept in solution with sterile water (500 mg/kg) and refrigerated. The salicylates were injected after being brought to room temperature. A 1.5 cc blood sample was taken from the external jugular vein of each of the three animals. Salicylate blood levels were established using the Trinder[29] method. Table 1 presents salicylate blood levels for these animals. The median level was 65.3 mg/100 ml. The 400 mg/kg dose was selected because it was the maximum the chinchilla could tolerate without exhibiting excessive side effects or dying.

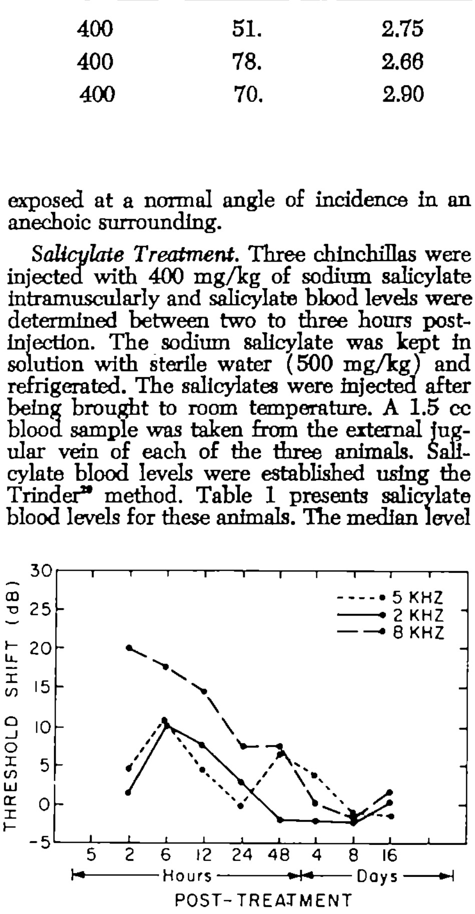

Fig. 1. Median threshold shifts as a function of time after salicylate injection (400 mg/kg) for the .5, 2 and 8 kHz test frequencies.

EXPERIMENTS

EXPERIMENT 1: SALICYLATE

Five chinchillas were injected with 400 mg/kg of sodium salicylate and their auditory thresholds measured at two hours postinjection and followed at regular intervals through 16 days.

Results. The median threshold shift at selected frequencies as a function of

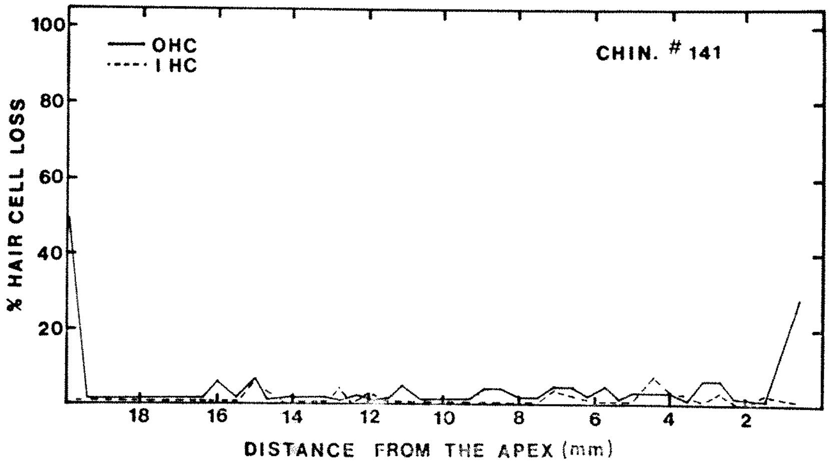

Fig. 2. The typical cochleagram seen from chinchilla receiving 400 mg/kg sodium salicylate.

time after injection is illustrated in Figure 1. The median $TTS_{max}=21$ dB and occurs at 8 kHz at the first postinjection test (two hours). The range of threshold shifts at all frequencies was 0-28 dB. The time at which TTS_{max} occurred was variable, but generally was from 2-6 hours after salicylate injection, occasionally as late as 12 hours postinjection. TTS as a function of frequency was generally irregular, but there was a tendency toward larger TTS at the higher frequencies. The magnitude and duration of the threshold shifts are consistent with the experiments described in the introduction. The cochleas from these animals are interesting. Figure 2 illustrates the cochleagram from an animal which was typical of the group. In general, all animals exhibited an average loss of less than 10% of outer and inner hair cells throughout the entire cochlea. Only one animal showed any localization of the lesion in the middle area of the cochlea. This loss amounted to slightly more than 10% outer hair cell loss between 6-12 mm from the apex of the cochlea. This degree of loss did not manifest itself in the audiometric data. While these patterns of hair cell loss appear to be small they certainly are outside the range of normal and one has to conclude that the salicylate injection did have an effect on the cochlea.

EXPERIMENT 2: SHORT TERM CONTINUOUS NOISE COMBINED WITH SODIUM SALICYLATE

Eight chinchillas were exposed to 95 dB, 2-4 kHz octave band noise for one hour. AER thresholds were obtained at .5, 1, 2, 4 and 8 kHz and followed from two hours postexposure through 31 days. In addition, thresholds at .5 hours postexposure were obtained at 4 kHz. Five additional chinchillas were injected with 400 mg/kg sodium salicylate. Two and one-half hours after injection, the thresholds were measured with the AER and the animals were exposed to the 2-4 kHz continuous noise band at 95 dB for one hour. The animals were followed with the AER for 31 days. The audiometric data from the combination animals were compared to the noise-alone animals.

Results. Group median threshold shift resulting from exposure to the short term continuous noise (squares), the 400 mg/kg sodium salicylate (circles), and the combination of these agents are shown for the 4 kHz test frequency in Figure 3. The 4 kHz frequency was chosen as typical of the high frequency TTS configurations. Lower frequencies (<2 kHz) showed less than 10 dB shifts for the individual as well as the combined agents. Care must be taken in reading the graph because there are two time bases: the

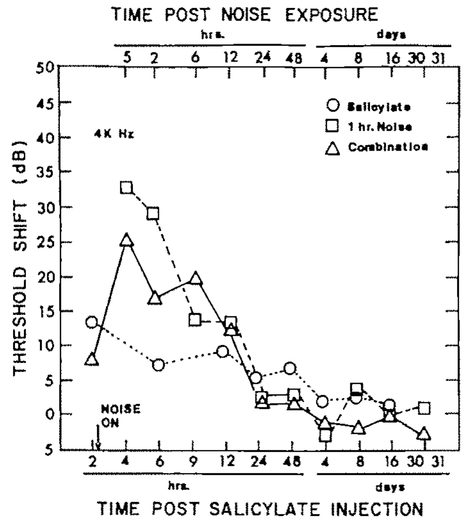

Fig. 3. Median threshold shifts at 4 kHz resulting from exposure to short term continuous noise alone; 400 mg/kg sodium salicylate alone; and a combination of these two ototraumatic agents.

lower base, time postinjection, refers to the salicylate and combination groups; the upper base, time postnoise, refers to the noise and combination groups. At lower frequencies, the combination treatment resulted in threshold shifts closely approximating those of the salicylate alone. Conversely, at 4 kHz (Fig. 3), the threshold shift resulting from the combination treatment approximated that of the noise alone, with no apparent contribution from the 7-14 dB threshold shift produced by the salicylate alone.

Figure 3 is interpreted to indicate that the TTS resulting from a combination of sodium salicylate and octave band noise is determined by the ototraumatic agent producing the greatest shift at a particular frequency. Out of the eight chinchillas exposed to the 95 dB octave band of noise alone, only two showed excessive hair cell loss. In the worst case, losses were about 15% in the apical 6 mm of the cochlea for both inner and outer hair cells. Part of this loss would be anticipated in normal control cochleas but would be confined primarily to the uppermost 3 mm of the cochlea. The remainder of the cochleas were normal, showing only very small hair cell losses (<3%) with greater losses being seen (10-20%) at the extreme apical 2-3 mm of the cochlea.

Combining this noise paradigm with the sodium salicylate produced the following histological results: none of the animals showed any excessive hair cell loss over and above that seen in the noise or drug-alone groups. At best, the histological effect is simply additive, yielding a low level hair cell loss throughout the entire cochlea. Figure 4 shows a cochleagram typical of this combination group. The remainder of

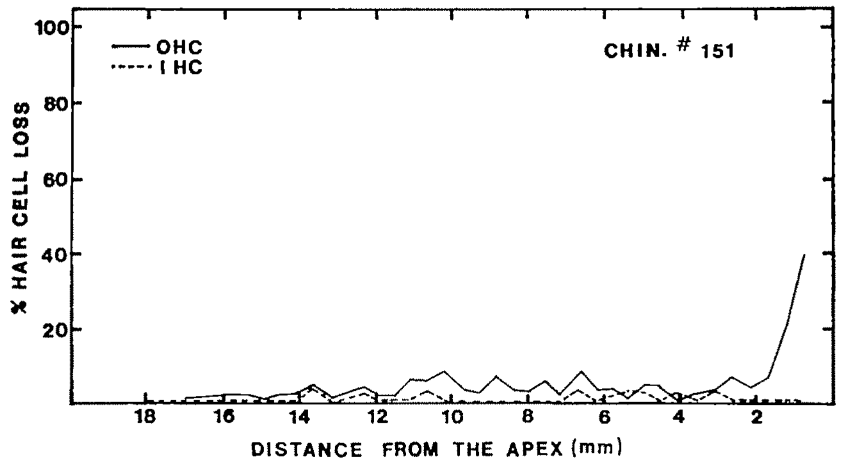

Fig. 4. Typical cochleagram from the group of chinchillas exposed to a combination of sodium salicylate and short term 95 dB octave band of noise.

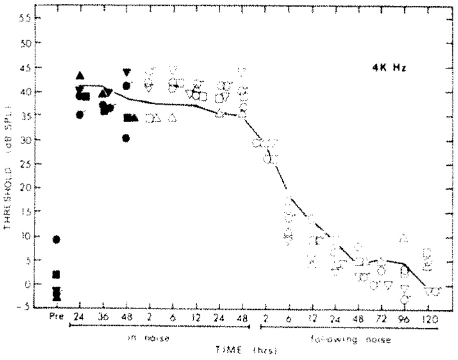

Fig. 5. The auditory evoked response thresholds at 4 kHz for chinchillas exposed to an asymptotic threshold shift-producing noise. Filled symbols refer to the individual data prior to 400 mg/kg salicylate injection. Solid line refers to the median threshold for the group of noise-only animals.

the animals in this group were very nearly identical.

EXPERIMENT 3: LONG TERM NOISE EXPOSURE COMBINED WITH SODIUM SALICYLATE

Two chinchillas were exposed to a continuous octave band of noise (4 kHz CF) at 80 dB SPL for 96 hours. The animals were removed from the noise environment for approximately 20-minute intervals at 24, 36, 48, 50, 60 and 72 hours following their introduction to the noise. Thresholds were obtained at test frequencies of 1, 2, 4 and 8 kHz; after each test, the animals were immediately returned to the noise environment. After 96 hours, the animals were removed and immediately tested for thresholds and then followed for a 31-day recovery period with the AER testing. A third animal was run through the identical paradigm except that it received a sterile saline injection (.8 cc/kg) at 48-hour break point of the exposure.

Five additional chinchillas were noise-exposed as described above, with the exception that this group received 400 mg/kg injections of sodium salicylate just after the 48-hour AER test period.

Results. The results at 4 kHz for the noise and combination groups are shown in Figure 5. The solid line is the median of the three noise-alone animals. The symbols refer to individual chinchilla. At the lower audiometric frequencies (<2 kHz), the noise-alone animal developed less than 10 dB TTS; at 4 kHz, there is approximately 40 dB TTS. When the animals are at asymptotic TTS, the administration of sodium salicylate had virtually no effect at the high frequencies (where sensitivity was most altered by the noise) and had a 10 dB effect at the lower frequencies.

Several additional points can be made from the data. 1) There is a consistent overshoot in the growth to asymptote; *i.e.*, the threshold after 24 hours exposure to noise is greater than at any other test time for individual animals. 2) All animals recovered to within 5 dB of their preexposure levels by 48 hours postnoise exposure. 3) Threshold variability is less during an ATS state than it is in a recovered postexposure condition. In addition, it should be noted that the single animal that received the saline injection behaved identically to the noise-only animals.

The animals exposed to the ATS noise-alone paradigm displayed a low level loss of hair cells throughout most of the cochlea (10-15%). Two animals from this group showed spotty lesions amounting to 40% over .25 mm areas of the cochlea. A similar noise exposure paradigm reported by Eldredge *et al*[21] also yielded relatively small hair cell losses throughout the cochlea with occasional larger isolated lesions.

When the ATS paradigm is combined with the salicylate treatment, no noticeable increment in loss is discernable. Only a single animal showed an excessive lesion (outer hair cells) and this occurred in the extreme base of the cochlea. The loss amounted to 60% outer hair cells between 14.5 and 16 mm from the apex. The remainder of the animals were not remarkable.

EXPERIMENT 4: IMPULSE NOISE COMBINED WITH SODIUM SALICYLATE

Five chinchillas were exposed to 50 impulses of 158 dB SPL, with a 50 μsec positive overpressure duration,

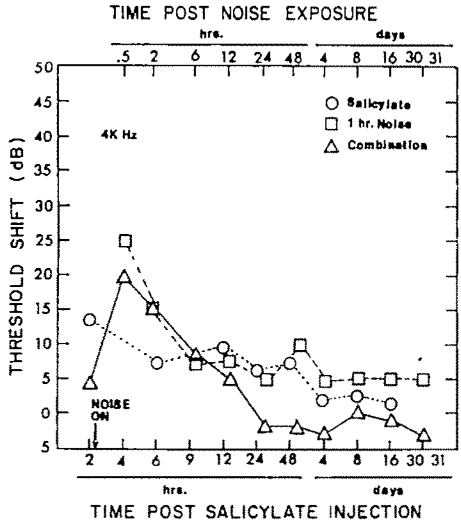

Fig. 6. Median threshold shifts at 4 kHz resulting from exposure to 158 dB impulse noise; 1/minute for 1 hour; sodium salicylate 400 mg/kg, and a combination of these two agents.

presented 1/min. The impulses had a blast wave profile described by:

$$p \sim (1 - t/t_A) \exp(-t/t_A)$$

where t_A is the duration of the initial positive overpressure. Animals were tested at regular intervals before and after exposure, through 30 days.

Five more chinchillas were injected with 400 mg/kg sodium salicylate. AER thresholds were obtained before, and two hours after, injection. Following the two-hour test, the animals were exposed to 50 of the impulses described above.

Results. The median threshold shifts for the impulse noise, salicylate and combination groups at 4 kHz are shown in Figure 6. The lower abscissa refers to time postinjection for the salicylate and combination groups and the upper abscissa refers to the postnoise exposure for the noise and combination groups.

Exposure to the impulses alone produced maximum TTS at the first postexposure test period. Median TTS_{max} varied between 5-15 dB for $.25 \leq f \leq 1$ kHz and between 20-30 db for $2 \leq f \leq 8$ kHz. Recovery was monotonic and complete with little or no PTS by 30 days postexposure.

Median threshold shifts at two hours postnoise exposure for the combination group varied from 7 dB at 2 kHz through 22 dB at 8 kHz. In general, the TTS frequency profile for both the combination group and the impulse noise-alone group reflects the high frequency loading (8-10 kHz) of energy in the impulse noise burst. The clearest comparison between these two groups is presented in Figure 7 where the median TTS_{max} is plotted across all frequencies, regardless of the time it appeared.

The cochleagrams from these two groups of animals followed a similar pattern to that already presented. The impulse noise-alone produced either a severe outer hair cell lesion that was localized to the extreme basal 4 mm of the cochlea or no significant hair cell loss at all. When the impulse noise is combined with the salicylate treatment, the primary difference in the cochleagrams was the general low level scat-

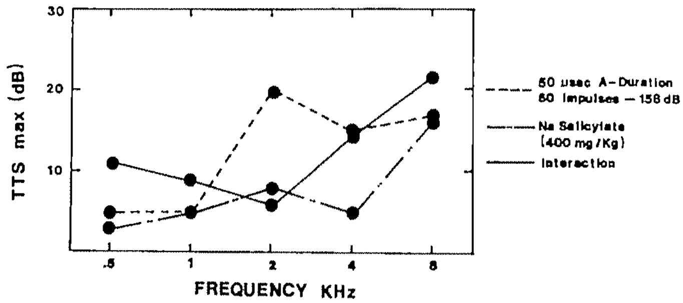

Fig. 7. The maximum median threshold shift for chinchillas exposed to the impulse noise alone; the sodium salicylate alone; and the combination of these agents, irrespective of the time TTS_{max} occurred, as a function of frequency.

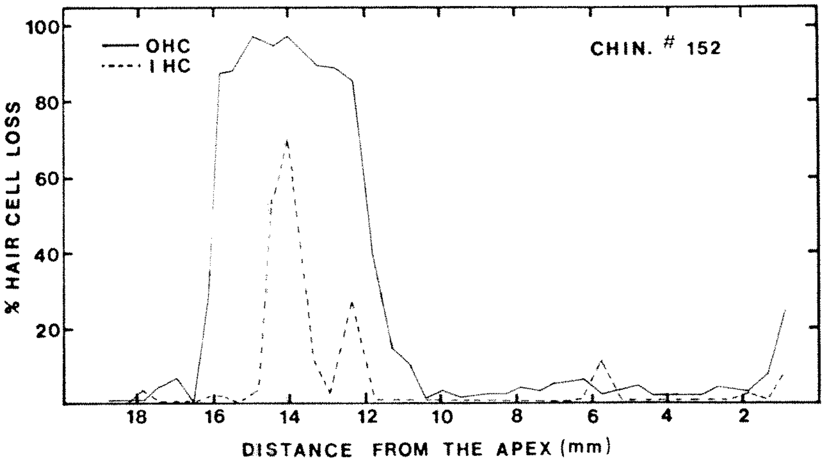

Fig. 8. Example of a cochleagram seen in the chinchillas exposed to a combination of impulse noise and sodium salicylate.

tered loss of hair cells throughout the cochlea or an expanded basal lesion similar to that seen in the noise-alone condition. A sample cochleagram from one animal in the combination group is shown in Figure 8.

Figure 9 illustrates three surface preparations of the sensory epithelia. The upper micrograph a) illustrates hair cell loss, both inner and outer, from a chinchilla receiving only sodium salicylate, while b) and c) are from a chinchilla that received both impulse noise and salicylate in combination. The severe defect visible in (c) is typical of impulse noise exposures, while the smaller scattered lesions such as are seen in (b) are more typical of the losses seen following salicylate administration. Regardless of the ototraumatic agent, the scarred end states of the sensory epithelium differed primarily in the extent and location of the lesion.

The results of the impulse/salicylate combination were not as clear as in the previous two studies, *i.e.*, at .5, 1 and 8 kHz the TTS_{max} in the combination group approximated the TTS_{max} of the ototraumatic agent producing the TTS_{max}, while at the midfrequencies, 2 and 4 kHz, the combination group sustained significantly less TTS (8-15 dB) than the noise-alone group. Nevertheless, the conclusion from this experiment is similar to the previous two; the mechanism of TTS production from impulse noise and salicylates does not appear to be potentiating or even additive.

DISCUSSION

The salicylate blood level reported by Mitchell *et al*[22] following injection of 545 mg/kg sodium salicylate in guinea pigs was found to be about 48 mg/100 ml. This is significantly smaller than the 65 mg/100 ml obtained in this study on the chinchilla injected with 400 mg/kg. This difference may reflect species differences in salicylate absorption or perhaps it more likely reflects a difference in procedure. Mitchell *et al*[22] used sodium pentobarbital with urethane as an anesthetic and the animals were respirated. Sodium pentobarbital is known to inhibit respiration, reduce oxygen consumption and, generally depress a wide range of biological functions in mammals including heart rate and blood pressure. The chinchillas reported here received the salicylates while awake and were not anesthetized until blood samples were taken.

The AER threshold shifts produced by the intramuscular injection of sodium salicylate in the chinchillas were found to be quite variable in magnitude, time course and frequencies affected. However, the variability is probably due to the chinchillas' reaction to salicylate rather than experimental procedures. Consequently, this variability

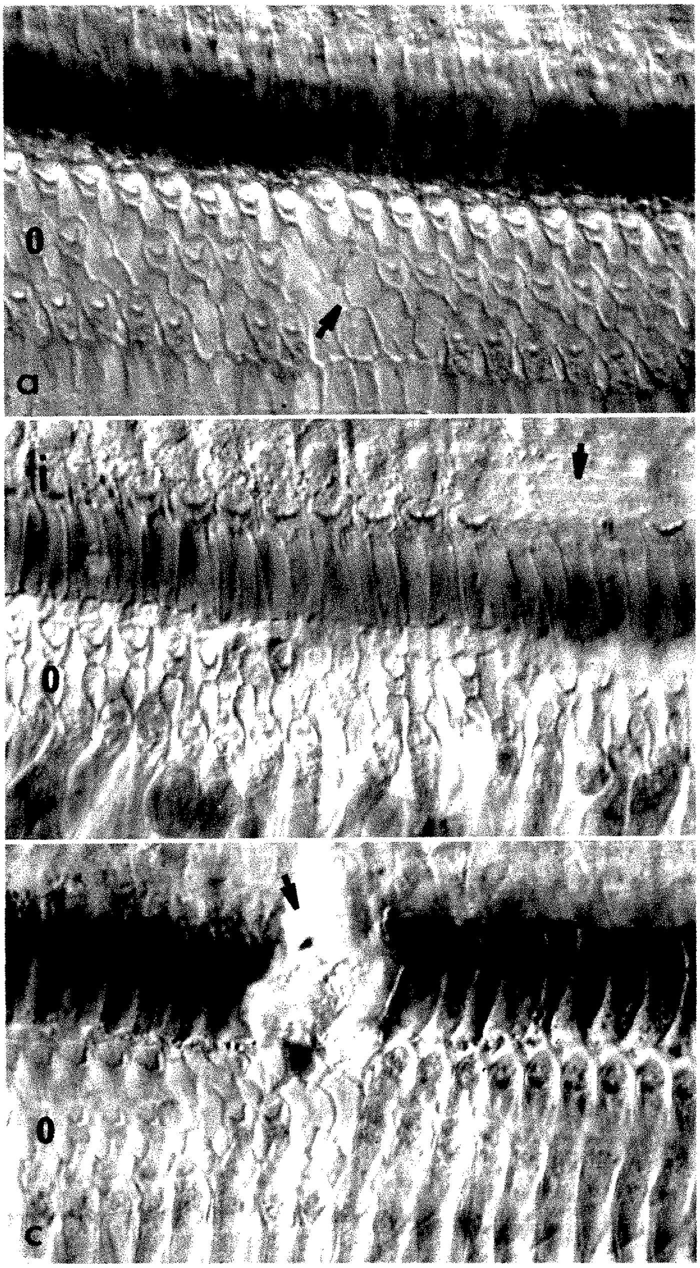

Fig. 9. Differential interference contrast micrographs of the organ of Corti seen in the surface preparation illustrating: a) a lesion in the animals receiving only sodium salicylate; b) a small lesion in the impulse noise/sodium salicylate combination group; c) a severe defect typical of the type produced by the impulse noise from the impulse from the impulse noise/sodium salicylate combination group.

may also account for conflicting reports of the configuration of the "salicylate audiogram" in man.

The chinchillas exposed to the various noise environments yielded hair cell losses that were in agreement with what was anticipated on the basis of previous experiments in our laboratories and other studies in the literature. The result of the administration of sodium salicylate in a dose of 400 mg/kg generally produced in each cochlea scattered losses throughout the entire cochlea. These losses were greater than from nontreated animals. When the two ototraumatic agents were administered in combination, the results across all the experiments described above showed a simple superposition of hair cell loss, *i.e.*, one could anticipate the interaction lesion by combining the "typical" cochleagram from the noise-alone animals with the "typical" cochleagram from the salicylate-alone animals. The audiometric and histological results, unlike the results with aminoglycosides, argue against a potentiation between sodium salicylate and various noise exposures in the chinchilla.

Based on the above data from the three segments of this investigation, it may be concluded that, at least for chinchillas, when sodium salicylate and noise are administered so that the respective threshold shifts overlap in time, the resultant hazard to the auditory system is not increased over that produced by either agent alone. This is a relatively important conclusion and we are cognizant that it is based on limited combinations. However, we have tried to optimize the potential for an interaction by using large doses of salicylate and three entirely different noise exposures, each bordering on the threshold of permanent damage.

These results suggest that the hazard faced by persons exposed to noise following salicylate ingestion is no greater than from either the noise or the salicylate alone. This finding has implications for not only the large arthritic population in our working force, but also, since salicylate is readily transferred to fetus via the placenta,[23,24] some concern for infants placed in the nonhazardous sound environment of incubators may be alleviated.

Of course, care must be exercised when inferring from an experimental animal to man; however, in this study the experimental design was chosen to maximize the potential for interaction and yet no interaction was found. Furthermore, when discrepancies have been found between results of noise experimentation on chinchilla and man, the chinchilla has consistently been found to be more susceptible to noise. These considerations suggest that the hazard to the auditory system for a given noise environment is not increased by salicylate ingestion.

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EXPERIMENTAL DIABETES AND THE INNER EAR

A PROPOSED BIOLOGIC MODEL

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SUMMARY — Experimental diabetes was induced in 28 healthy chinchillas by the intravenous injection of Streptozotocin.® Five chinchillas were used as controls. It was noted that a dose of 60 mg/kg body weight produced a noninsulin-dependent diabetes in adult chinchillas of mean weights of 393 gm. The chinchilla is proposed as a suitable animal model for the study of experimental diabetes because of the many attributes it possesses. A method of producing experimental diabetes is described. A method of anatomical display was utilized that allowed a detailed longitudinal study of the entire cochlear partition without sacrificing the stria vascularis and Reissner's membrane. The study did not yield any new histopathologic data concerning the nature of diabetes in the inner ear. In all likelihood this is, among other things, a factor of the mild severity of diabetes induced and the short duration of this study.

More than a century ago, Jordao[1] suggested a relationship between diabetes mellitus and hearing loss. Since that time several authors[2,3] have mentioned a possible relationship on the basis of clinical data or necropsy findings. Other authors[4-6] have suggested, on the basis of clinical observations, that diabetes affects the inner ear early in its onset and that not unlike the retina, the renal glomerulus and other "target" tissues, the resultant disturbances in inner ear function may be recognized before the disease becomes manifest clinically. The latter concept is especially intriguing when one considers diabetes is a major disorder which sooner or later affects at least 5% of the population of the so-called "developed" regions of the world.

The recent studies of Quick et al[7] which show striking ultrastructural, pharmacological, immunological and clinical pathological similarities between the renal glomerulus and the stria vascularis, strongly suggest by inference that some of the changes noted in the pathophysiology of the diabetic renal glomerulus might have their equivalents within the cochlear partition.

Studies of distribution of energy stores (primarily glucose and glycogen) within the inner ear attest to the primary role of carbohydrate as the main source of energy producing processes.[8,9] The dynamic influence of hormones (primarily insulin) in control of these mechanisms throughout the body is well-known. The neuroendocrinologic implications of impaired metabolic pathways of carbohydrate metabolism manifest in diabetes throughout the nervous system must certainly affect a special sense organ as delicate as the inner ear.

One cannot have direct access to the inner ear in human beings during life to study the pathophysiology of diabetes. The scarcity of available necropsy material in humans, the time delays in processing fresh material, in addition to the obvious need to study the disease state in all its biophysiochemical dimensions suggest the need for alternative methods.

An animal model in which diabetes can be induced or one in which spontaneous diabetes has been observed seems appropriate for study. Adequate controls and precise assessments of altered function can be monitored under

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laboratory conditions. One finds a myriad of complicated pathophysiological derangements in diabetes. When one attempts to reproduce these within the laboratory animal, the dimensions of such an undertaking assume gargantuan proportions.

The principal animals which have formed the basis of most otologically oriented studies have been the guinea pig, cat, dog, mouse, chinchilla and monkey (not necessarily in that order). The field of otology has had no sustained input in the laboratory investigation of experimental diabetes. This is especially noteworthy in view of the dramatic new revelations about the etiopathogenesis of diabetes which have occurred during the past 15 years.

The purposes of this investigation are threefold: 1) to propose a satisfactory animal model in which diabetes can be artificially induced and maintained over a reasonable period of time; 2) to study the microscopic alterations of the cochlear partition as it is affected by diabetes; and 3) to attempt to stimulate a sense of urgency in our specialty for well-financed and well-disciplined studies of the relationship of diabetes to the inner ear.

With these purposes in mind, were one to propose a biologic model, certain attributes seem worthy of consideration:

1. The animal should have a reasonable life span, relatively free of adjunctive disease states such as spontaneous middle ear disease and premature atherosclerosis among others.

2. It should be capable of having the diabetic state induced and maintained over a sufficient period of time to allow various aspects of the disease to be assessed in both a qualitative and a quantitative manner.

3. The animal should have been the basis of enough prior investigative study that many of its "norms" will have been established.

4. The audibility range of the experimental animal should grossly resemble that of man.

5. The diabetes produced should have some gross similarities to that observed in man.

6. The animal should be relatively inexpensive to purchase, maintain, and be available in suitable quantities.

Although the above list is probably incomplete, it is fairly obvious that no animal, at present, possesses all these attributes. A special strain of inbred Chinese hamsters in which diabetes has occurred spontaneously appears to be the most enthusiastically studied animal at this time from the standpoint of the general investigations of the etiopathogenesis of diabetes.[10] Its limited availability, in addition to the fact that it has not been the subject of any published otological research to date, will perhaps restrict its use in our specialty for some time.

An animal which meets most of the aforementioned criteria, except those related to diabetes per se, is the chinchilla. According to Miller,[11] basic determinations of electrophysiological norms of cochlear potentials, cortical and nuclear activity, and VIII nerve studies have all been performed in the chinchilla. There are abundant sources of literature in support of these studies.[12-17] Furthermore, Miller and Luz[18,19] have demonstrated the chinchilla's suitability as a subject for behavioral studies of auditory function. When compared with the cat, guinea pig and rat, the chinchilla's audibility curve is more similar to that of man.[11]

Chinchillas have a life span of more than 15 years and Bohne et al[*20] have demonstrated some preliminary evidence that there is relatively little loss in auditory acuity as measured by electrophysiological and anatomical means in chinchillas that have aged. Other attributes mentioned by Miller are their relative freedom from middle ear infections, their modest purchase price, and low maintenance cost as compared with cats, dogs or monkeys. The middle ear is also readily accessible to surgical ap-

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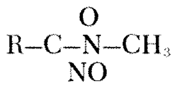
[*] Bohne, BA, Eldredge, DH, and Miller JD: Unpublished data.

proaches and the chinchilla tolerates barbiturate anesthesia well.

The scope of any laboratory investigation of experimental diabetes of necessity encompasses some broad biochemical, biophysiological concepts. The biochemical dimensions of this study are purposefully restricted.

For this study, the induction of the "diabetic state" has consisted of qualitative and quantitative determinations of glucose levels of blood and urine which were persistently and significantly elevated above the norms. Where there was significant glycosuria, qualitative determinations of ketone bodies were performed. The term "persistent" was interpreted for purposes of this study to extend for one month or longer. This limited concept of the "diabetic state" was decided upon by an interest in the early changes which might be observed anatomically in the latent and early manifest stages of the disease as well as by the time and fiscal limits imposed upon the study.

The drug used for the artificially-induced diabetes was Streptozotocin,® an antibiotic extracted from *Streptomyces acromogenes*. The Streptozotocin® for this study was in a highly purified form.[*] The drug was demonstrated by Vavra[20] and later by Rakieten et al[21] to exhibit a diabetogenic action when injected intravenously in dogs and rats. The drug, a crystalline material, is a nitrosamine derivative with an empirical formula of $C_{14}H_{22}N_5O_{12}$ containing the grouping:



$$R-C-\overset{O}{\underset{NO}{N}}-CH_3$$

Some early controversy existed as to the mechanism of its diabetogenicity. Junod et al[22] demonstrated that the drug produces a rapid and specific cytotoxic action upon pancreatic beta cells which is irreversible and only partly resembles the action produced by alloxan, a well-known diabetogenic agent. Their study revealed that the action of Streptozotocin® occurs early after one hour with intense necrosis strictly limited to beta cells evident at seven hours by both light and electron microscopy. Additional advantages of Streptozotocin® over alloxan are that with alloxan there is an extremely narrow margin between the diabetogenic and generally toxic and lethal dose. There appears also to be greater specificity for the destruction of beta cells with Streptozotocin® than alloxan. In rats, diabetes has been produced by Streptozotocin® with doses as low as 25 mg/kg and of greater severity with 100 mg/kg. The LD_{50} in rats is reported to be 130 mg/kg.

To assess the possible damage of the induced diabetic state upon the inner ear, a study of the cellular morphology was undertaken. The anatomical focus has been a study of the cytoarchitecture of the cochlear partition by the surface or longitudinal method. This method has proven an excellent modality to observe minute comparisons of normal ears as well as ears damaged by anoxia, acoustic trauma and ototoxic drugs among others. The technique is an outgrowth of a method originally suggested by the elaborate drawings of Retzius,[23] revived by Neubert,[24] and further refined by many others including Engstrom et al[25] and Hawkins.[26] More recently, there has been the addition of a new histological technique by Bohne[27] that forms the basis for the anatomical observations of this investigation.

The specific advantages of Bohne's technique over others for this study include that it allows a study of the entire organ of Corti in a longitudinal view with selective sectioning of injured areas for examination at different angles and at higher magnification including electron microscopy. Also previous techniques required the removal of Reissner's membrane and the stria vascularis prior to longitudinal study. Bohne's technique minimizes opportunities for introducing artifactoral changes from excessive handling of the unsupported tissues and reduces sampling error in sections for electron microscopic study. Dead cells and debris from prior injury are likewise preserved for viewing. Because of the imposed limits of time and circumstance, no attempt was made in this study to obtain definition beyond the limits of light microscopy. For similar reasons, no attempts were made to study the morphology of the vestibular portion of the membranous labyrinth.

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[*] Provided by the Upjohn Company (Lot 9681-GGS 118FI-U-9889), Kalamazoo, MI.

METHODS AND MATERIALS

Induction of Diabetes in Chinchillas. Twenty-seven adult chinchillas were made diabetic by the intravenous injection of Streptozotocin® after an overnight fast. The animals were all healthy with good pinna reflexes. Five animals were used for controls. The animals were obtained from a chinchilla ranch in Iowa. Weights varied between 366 gm and 555 gm. The mean weight was 393 gm. There were 23 males and 4 females. Their ages at the time of injection ranged from 4 to 13 months.

For the injection of the Streptozotocin® the animal was first sedated with ketamine hydrochloride. The ventral aspect of the body between the jaw and forelegs was shaved and prepped. A ventrolateral incision was made through skin and superficial fascia in the lower neck to expose the external jugular vein. The Streptozotocin® was prepared fresh within five minutes prior to injection. The desired amount of Streptozotocin® dissolved in 0.5 ml (prepare 0.6 ml) of citrate buffer (pH adjusted to 4.50) was injected into the external jugular vein. The incision was sutured with 4-0 silk interrupted sutures. Seven animals received an injection of Streptozotocin® at a dosage of 100 mg/kg; 15 animals received 60 mg/kg; 2 received 55 mg/kg; and 2 received 35 mg/kg.

Fasting samples of blood and urine were obtained prior to the injection of Streptozotocin.® Urine samples were obtained by sterile catheterizations of the bladder with qualitative tests for sugar using paper indicators (Combistix®). Ketonuria was also monitored by paper indicators (Ketostix®). Blood samples were obtained by either excising the tip of the tail or incising the ventral surface of the tail. The chinchilla has no accessible superficial veins suitable for venipuncture. The quantitative determinations of blood sugar were performed by using the glucose oxidase assay method adopted from the Nelson-Somogyi procedure.[23] The urine was checked for glycosuria on the first day after the injection, again on the fifth day and at biweekly intervals thereafter. Blood and urine sugars were taken again immediately prior to sacrifice (Fig. 1).

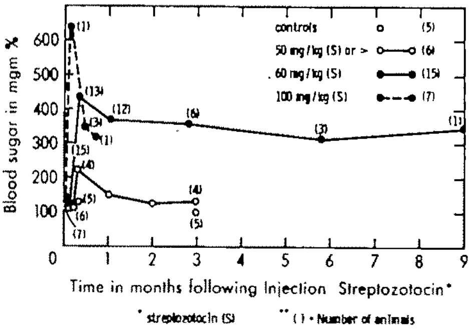


Fig. 1. Blood sugar levels of controls and induced diabetic chinchillas following injection of Streptozotocin®.

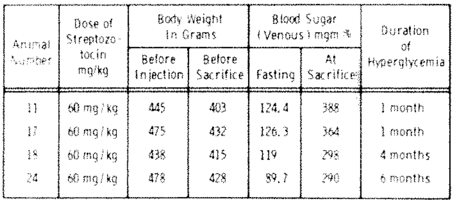
Preparation for Anatomical Study. An abbreviated description of the method of histologic study is presented inasmuch as a detailed description of the technique has been published in the recent literature.[27] The technique consists of perfusion of the labyrinth with a fixative (1% osmium tetroxide in Dalton's buffer) through the perilymphatic spaces in the living animal anesthetized with Dial® with urethane (0.5 ml/kg body weight) injected intraperitoneally. After fixation, the animal is sacrificed and the specimens are removed from the skulls, rinsed, dehydrated, and embedded as intact cochlea in plastic (araldite). The entire cochlear duct is preserved by this technique including the stria vascularis and Reissner's membrane. Following polymerization of the plastic, the bony wall of the otic capsule is trimmed from the specimen along with the excess araldite, using picks and razor blades. The cochlear duct is then separated from the modiolus in half turns. These cut specimens are reimbedded. The plastic is allowed to polymerize again and each section is trimmed carefully, removing all bone present above Reissner's membrane or below the basilar membrane. A special effort is made to trim the araldite in the scala tympani as close to the basilar membrane as possible. A final embedding is made in which the trimmed specimens are arranged in a serial manner in a thin block of araldite with the basilar membrane close to the bottom of the container. Prior to the second embedding, samples of stria vascularis and spiral ligament can be separated from the remainder of the cochlear duct and embedded flat in a layer of araldite so that the vasculature of these structures can be studied.

Once the entire organ of Corti has been surveyed, the precise area of the lesion can be isolated and radial, horizontal or tangential sections made using the ultratome for viewing by electron microscopy.

Photomicrographs of the phase contrast observations were made using the Wild phototube attachment in the manner described by Bohne.[27]

RESULTS

In this study there were initial attempts to induce diabetes in chinchillas with alloxan. The efforts were soon discontinued due to a lack of success in inducing diabetes. Subsequently, attempts were made to induce diabetes by the use of a single intraperitoneal injection of Streptozotocin® as de-



Animal Number	Dose of Streptozo-tocin mg/kg	Body Weight In Grams		Blood Sugar (Venous) mgm %		Duration of Hyperglycemia
		Before Injection	Before Sacrifice	Fasting	At Sacrifice	
11	60 mg/kg	445	403	124.4	388	1 month
17	60 mg/kg	475	432	126.3	364	1 month
18	60 mg/kg	438	415	119	298	4 months
24	60 mg/kg	478	428	89.7	290	6 months

Fig. 2. Comparative data of four chinchillas with induced diabetes whose cochlear anatomy is described.

scribed by Marshak;[29] we were unable to duplicate his results of maintaining the diabetic state utilizing his technique.

All animals injected with 100 mg/kg of Streptozotocin® died within one month (Fig. 2). Most died within the first five days of ketoacidosis and its complications. The animals which received 50 mg/kg or less did not maintain blood sugar levels of 300 mg% or more for as long as one month. For purposes of this study it was found that significant hyperglycemic levels could be induced and maintained with a minimum of complications and deaths with a dose of Streptozotocin® of 60 mg/kg of body weight. One animal maintained blood sugar levels of near 200 mg% for nine months.

For the study of the cytoarchitecture of the cochlear partition, four hyperglycemic chinchillas and two controls were studied. Two hyperglycemic animals were sacrificed at one month, one at four months and one at six months.

The phase contrast microscopic appearance of the inner ears in the hyperglycemic chinchillas was identical to that of the controls. The stereocilia on the outer hair cells were arranged in the typical W-shaped pattern (Fig. 3A). Outer hair cell bodies were not swollen and organelles had their usual distribution (Fig. 3B). The nonmyelinated nerve fibers within the organ of Corti had entirely normal appearances (Fig. 4).

Vessels below the basilar membrane and within the stria vascularis and spiral ligament were carefully examined for evidence of thickened basement membranes, vessel narrowing, etc. In the present series of animals, however, no lesions were visible by phase contrast microscopy in any of these vessels (Fig. 5A, B). Figures 3-5 are from one of the animals which was hyperglycemic for one month but the findings were similar in all specimens.

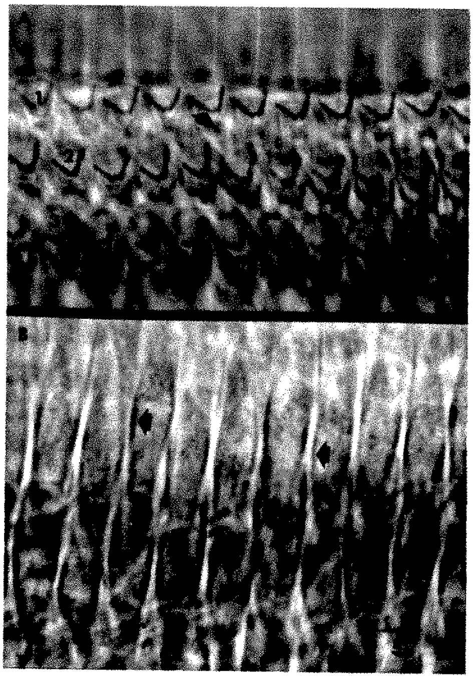


Fig. 3. A) Phase contrast photomicrograph showing normal W-shaped arrangement of stereocilia (arrows) on three rows of outer hair cells (1, 2, 3). B) Peripherally-arranged mitochondria are visible as small dark dots (arrows) adjacent to plasma membranes of outer hair cell bodies. Note uniform shape and orientation of individual hair cells.

DISCUSSION

The chinchilla appears to possess many of the attributes of a good biologic model in which to observe the effects of induced diabetes upon the inner ear. It is acknowledged that maintenance of hyperglycemia and glycosuria is not synonymous with diabetes. Many other parameters of the disease need simultaneous monitoring, for example: a) duration and severity of disease; b) genetic factors which were not accounted for in this model; and c) response of the animal to glucose challenge, immunoreactive insulin levels,

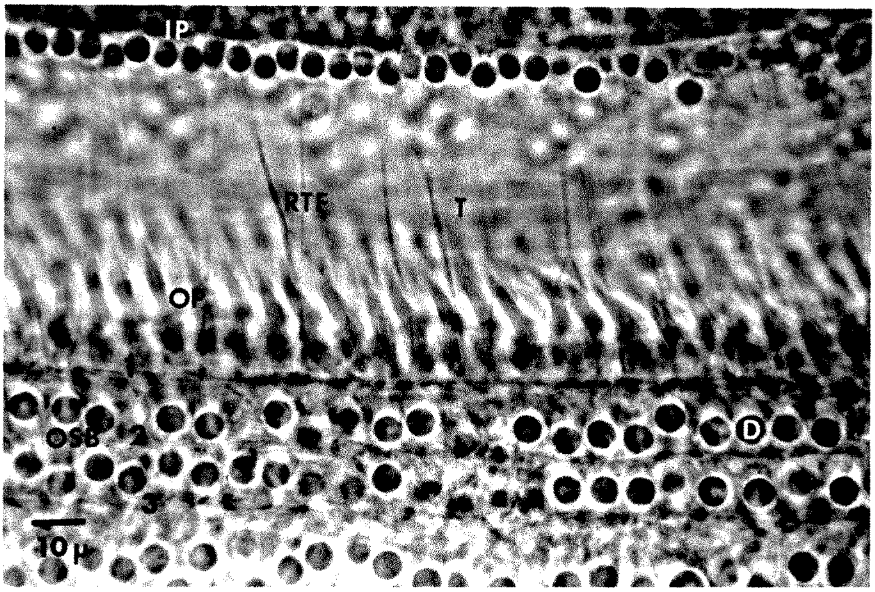


Fig. 4. Radial fibers (RTF) can be seen crossing tunnel space (T) from area near inner pillar bases (IP), exiting from tunnel between outer pillar bodies (OP) and joining outer spiral bundles (OSB 1, 2, 3) of nerve fibers beneath the three rows of outer hair cells. Nuclei of Deiters' cells (D) can be seen between outer spiral bundles.

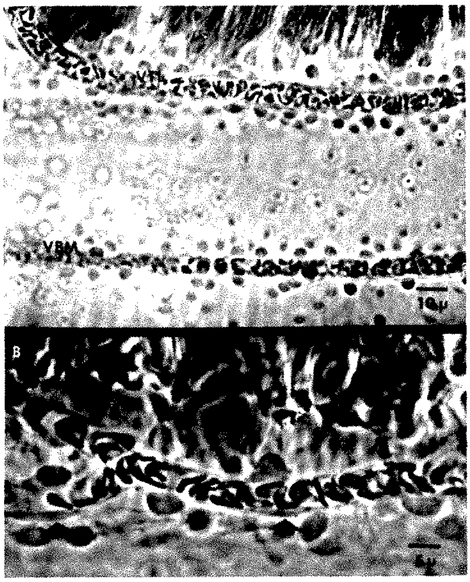


Fig. 5. A) Red blood cells fill vessel of the tympanic lip (VTL) of osseous spiral lamina below inner hair cell and vessel of basilar membrane (VBM) beneath tunnel space. B) Higher power photomicrograph of vessel of tympanic lip showing flattened endothelial cell nuclei (arrows) and uniform thinness of walls.

free fatty acids and significant changes in body weight.

The method of inducing diabetes by the intravenous injection of Streptozotocin® is a reliable one. Whereas there has been determined no optimum dosage for maintaining a "permanent" state of hyperglycemia, an intravenous dose of 60 mg/kg appears to be sufficient for maintenance of significant levels up to nine months or more.

The Bohne technique of embedding and display of the cochlear partition is an excellent one that seems especially suitable for an inquiry of this nature. When one considers the type of lesion diabetes produces in other organs and tissues, the ability to examine simultaneously both the vasculature and sensory organ within the same specimen seems essential.

The fact that no unique anatomical lesions attributable to diabetes were observed in this study does not invalidate the basic considerations of the model. It is more likely a factor of the limited severity and duration of the diabetes produced.

The need for investigative inquiry

into the otologic implications of diabetes in the inner ear is an urgent and complex one that is a worthy endeavor for our most diligent study.

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BILATERAL ACOUSTIC NEURINOMAS

A CASE REPORT

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SUMMARY — A patient presented with complaint of increasing hearing loss in the right ear of five months duration. There was no hearing in the left ear as a result of previous surgery for resection of an acoustic neurinoma. Polytomes demonstrated a progressive erosion of the right auditory meatus. The patient underwent a right suboccipital craniotomy resulting in preservation hearing at a 30 dB level with 100% discrimination scores.

A 17-year-old Caucasian male high school student first presented at the Massachusetts Eye and Ear Infirmary on May 12, 1976 with a chief complaint of a gradual increasing hearing loss in the right ear of five months duration. Two years previously the patient had undergone suboccipital posterior fossa surgery for removal of a large (4.5 cm) acoustic neurinoma on the left side. A total left hearing loss and left facial paralysis followed this operation. A hypoglossal facial anastomosis quite successfully corrected the left facial paralysis. There was no family history of neurofibromatosis, an absence of café au lait spots, and no symptoms referable to other neurofibromata. X-rays of the internal auditory meati also demonstrated an enlargement on the right. Right auditory and vestibular testing, however, was normal. The CT scan showed a 4 cm lesion in the left cerebellopontine angle and suggestion of a small lesion on the right side (Fig. 1).

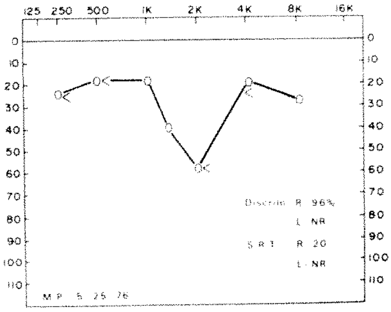

Fig. 2. Audiogram taken on May 25, 1976 prior to right suboccipital craniotomy.

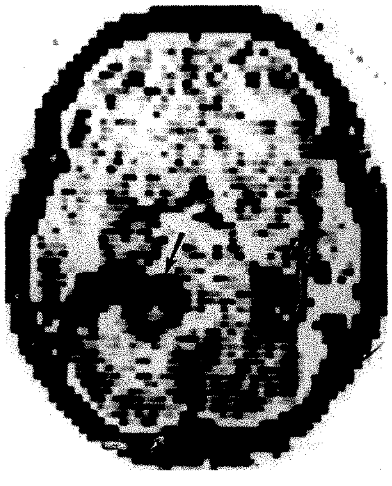

Fig. 1. CT scan study showing a 4 cm lesion (arrow) in the left cerebellopontine angle and suggestion of a small lesion on the right side.

Audiometry on May 25, 1976 demonstrated a 20 dB speech reception threshold with 96% discrimination as compared to normal hearing on this right side ten months previously (Fig. 2). There was no significant tone decay and the SISI test was positive at 2000 Hz.

Electronystagmography on May 24, 1976 demonstrated a definite caloric

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From the Harvard Medical School and the Massachusetts Eye and Ear Infirmary, Boston, Massachusetts.

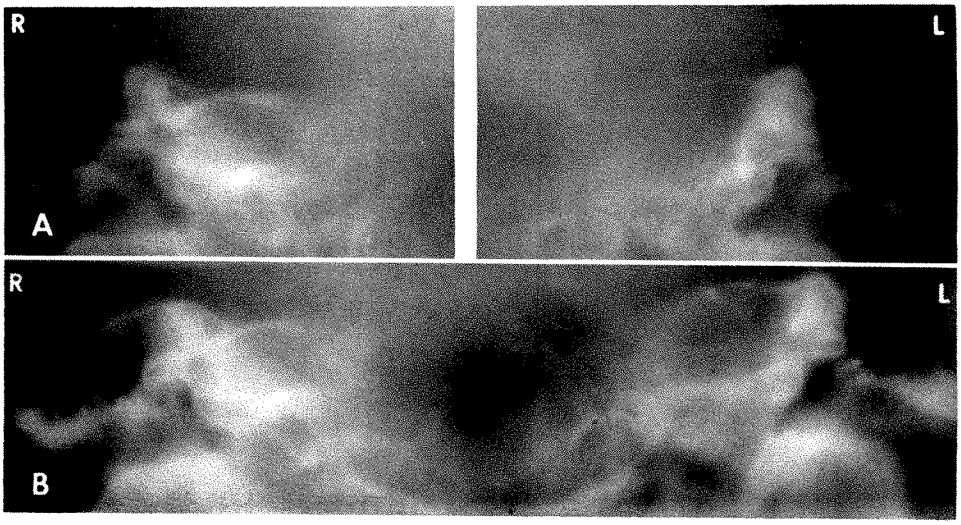

Fig. 3. Polytomes of the internal auditory meatus done on May 24, 1976 (B) demonstrate an increased expansion on the right side when compared to those of May 14, 1974 (A).

response on the right side preoperatively. There was more right beating nystagmus with the eyes closed as compared to the study of May 9, 1974. This is probably accountable by the fact that the left vestibular nerves were resected at the time the left acoustic neurinoma was resected on June 3, 1974. In conclusion, there was no significant change in the electronystagmography testing between the two dates.

Polytomes suggested a progressive erosion of the right internal auditory meatus when compared to films taken two years previously (Fig. 3). A CT scan was normal. A posterior fossa myelogram demonstrated a 1.5 cm filling defect adjacent to the right internal auditory meatus. The diagnosis of a contralateral acoustic neurinoma was thus established.

A conference which included the patient, his parents, an otoneurologist, a neurosurgeon and an otolaryngologist was convened in order to make a very difficult decision. Among the items under consideration were:

1. Do nothing and wait until the hearing dropped spontaneously before removing the tumor, even though his hearing loss had progressed rapidly on the opposite side. There was a possibility that he would retain serviceable hearing until he graduated from high school;

2. A middle cranial fossa approach in attempt to resect the tumor and preserve hearing;

3. The posterior suboccipital operation with an attempt for total removal of the tumor and preservation of the hearing;

4. The translabyrinthine operation with a resulting total loss of hearing, but a somewhat better possibility for preserving facial nerve function.

All present at the conference agreed

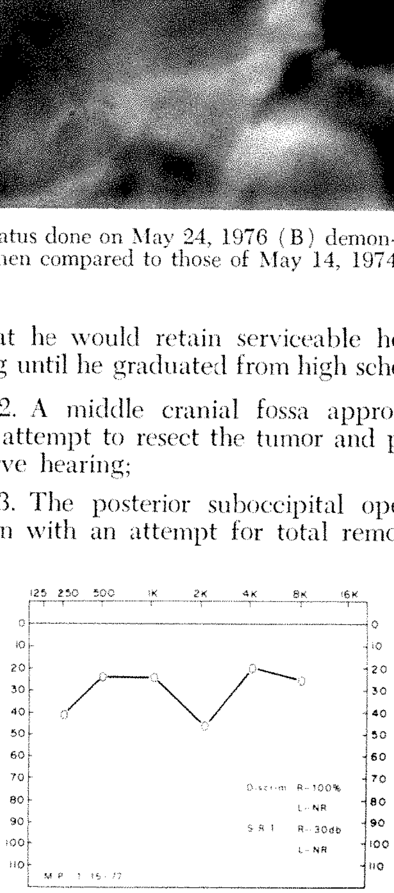

Fig. 4. Audiogram taken January 15, 1977 following right suboccipital craniotomy performed July 7, 1976.

that the suboccipital operation would be best as soon as possible following completion of his third year in high school. On July 7, 1976 the patient underwent a right suboccipital craniotomy. Total removal of a 1½ cm acoustic neurinoma which was moderately adherent to both the VII and VIII cranial nerves was accomplished with preservation of the facial and cochlear nerves along with their accompanying blood supply.

The morning following this surgery the patient was found lying in his bed with only mild discomfort, there was a moderate right facial weakness and he was listening to his radio. The facial weakness cleared spontaneously after two months. The hearing has remained at a 30 dB level with 100% discrimination score (Fig. 4).

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CURRENT CONCEPTS OF TUMOR IMMUNOLOGY
III. IMMUNE THERAPY

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SUMMARY — It is apparent that development of consistently effective methods of immunotherapy must await a more thorough understanding of the immune response to cancer. However, even those forms of immunotherapy which have been developed to date indicate a tremendous potential. It appears that immunotherapy may be most useful as an adjuvant to established forms of treatment. Surgery, radiation therapy and/or chemotherapy are used to remove all of the gross tumor, with immune therapy then employed to destroy the small foci of tumor which remain. As methods are developed which are effective in counteracting the immunosuppression of tumors, other means of immunotherapy may be found which are capable of destroying tumor cells while not affecting the adjacent normal tissue. Thus, the future of immune therapy holds great promise. As more is learned about the immune response to cancer, advances in therapy will certainly follow.

Much of the early work in tumor immunology focused on treating cancer patients with injections of tumor cells or extracts. In 1902, Von Leyden and Blumenthal[1] treated a series of patients with autologous tumor cell suspensions used as a vaccine. There was no objective evidence of improvement noted.

Even today there is very little objective evidence of positive responses to immunotherapy. Successes have been largely limited to the occasional isolated patient with a dramatic regression of tumor, not unlike those occasional spontaneous regressions which occur. In fairness, it should be noted that nearly all of the immunotherapy used thus far in humans has been utilized in patients with advanced disease. These are the patients most likely not to respond to immune therapy.

A major obstacle to effective immunotherapy is the suppressive action of the tumor itself. These "blocking factors" render all forms of active immunotherapy less effective. For this reason, the first step in developing an effective means of immunotherapy must be to develop methods of eliminating this suppressive action. One method available today is to remove the main tumor load using standard treatment modalities, and then institute immune therapy as an adjuvant in treating the small numbers of cells which remain.

A much more complex, though potentially more effective, method involves the removal or inhibition of blocking factors. Development of such a technique, however, must await a clearer understanding of the exact nature of these blocking factors. If they prove to be soluble tumor antigen as presently believed, methods for active or passive anti-blocking factor antibody production might successfully reduce their blocking effect (unblocking antibodies).

Another practical problem facing clinical researchers today is the lack of any one effective method for determining the competence of an individual's immune system.[2] It is frustrating and potentially hazardous to alter an

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This is the third of a series of papers by the authors on tumor immunology. The first and second appeared in the September-October and November-December, 1977 issues of the ANNALS.

individual patient's immune system without the capability of quantitatively assessing the status of that system before, during, and after treatment. Immune competence is inferred from the results of a battery of skin tests and *in vitro* assays, with no one test capable of distinguishing the immune competent from incompetent patient, much less quantitatively assessing the effects of treatment.

The following is a brief discussion of some ways in which immune therapy is being used today, and some methods which offer hope of success in the future.

IMMUNOPREVENTION

It appears that the use of immune therapy might be most effective when utilized as prophylaxis, as is common for polio and measles today. In this way, tumors might be prevented from developing beyond a few cells, since the immune system would have been previously sensitized and primed to destroy such a tumor. However, the multiplicity of tumor types found in humans, each apparently differing in antigenic determinants from other types, makes development of an effective preventative vaccine an unlikely short-term goal except in certain high risk patients (such as those with familial polyposis of the colon).

Nonspecific stimulation of the immune system offers greater promise for the immediate future. It could theoretically result in a simultaneous increase in resistance against all types of cancer in man by stimulating the immune system to an increased response against all foreign antigens. Such nonspecific stimulation with Bacillus Calmette-Guirin (BCG) or other similar agents has produced demonstrable inhibition of a variety of viral and chemical carcinogen-induced neoplasms in animals.[3,4]

Thus far there is little evidence available that nonspecific active therapy is an effective method of cancer prevention in humans. One of the few such studies reported thus far, however, did demonstrate a significant lowering of the incidence of acute leukemia in a group of children treated with BCG when compared to the controls.[5]

NONSPECIFIC ACTIVE IMMUNOTHERAPY

Nearly all of the experience to date with immunotherapy in humans has been with established tumors, most often in an advanced stage. Nonspecific stimulation of a cancer patient's immune system may, in some instances, result in a regression of such a neoplasm. Dr. Bradford Coley reported[6] the regression of an inoperable sarcoma in a patient who developed erysipelas. This encouraged him to develop a mixture of killed bacterial toxins which he injected directly into cutaneous carcinoma and administered systemically as well.

Subsequently, a variety of bacterial substances have been utilized to stimulate host resistance in a nonspecific way. BCG and *Corynebacterium parvum* are the most commonly used agents today. Though the exact mechanism is poorly understood, these agents appear to promote an increased immune response to a variety of antigens, including bacterial, viral, and tumor associated antigens.

Morton and associates[7] found in patients who were competent immunologically, that approximately 90% of cutaneous melanoma nodules injected directly with BCG regressed. In 20% of the immunologically competent patients, melanoma nodules at other sites also regressed. Though regression of the injected nodules may be due to a localized inflammatory reaction rather than a true immune response, the regression of noninjected nodules must certainly be attributed to an immune response.

As in other forms of active immunotherapy, the immunosuppressive action of a large tumor reduces the effectiveness of BCG in advanced disease. Therefore, several studies presently underway to evaluate the effectiveness of BCG as adjuvant therapy in the presence of minimal residual disease may give some insight into how effective this form of immune therapy will prove to be.

It should be pointed out, however, that the administration of BCG and *C. parvum* may result in significant fever and chills, particularly when administered parenterally. In addition, enhancement of tumor growth associated with BCG therapy has been reported,[8] as well as apparent depression of cellular immunity associated with repeated doses of BCG in animals[9] and humans.[10]

SPECIFIC ACTIVE IMMUNOTHERAPY

If nonspecific stimulation of the host immune system causes regression of tumor, then specific stimulation of that system with tumor cells might result in even greater responses. The most effective method of producing active immunity against a tumor in animals is to vaccinate the animal with small aggregates of viable tumor cells. Because this may not be entirely safe for use in humans, various ways of rendering the cells nonviable have been developed, including irradiation, freeze-thaw and mitomycin-C treatment.

In addition, attempts have been made to render the tumor cell vaccines more strongly antigenic. To this end, coupling of tumor cells with rabbit gamma globulin or treatment of the cells with neuraminidase or conconavalin-A has been used. In other experiments the vaccines have been used in conjunction with immunostimulants such as BCG, *C. parvum* or Freund's adjuvant.

Purified specimens of specific antigens may be a much safer and potentially more effective vaccine than whole tumor cells. Thus far, techniques for tumor antigen purification have not produced an ideal vaccine. Results with this form of immune therapy have been disappointing, probably because of immune suppression by the tumor. It would appear, however, that tumor vaccines may prove to be an effective form of therapy when used as an adjuvant in the presence of minimal residual disease.

PASSIVE IMMUNOTHERAPY

Passive immunotherapy consists of administering either humoral antibodies or sensitized lymphocytes to the cancer patient. Because the host immune system is commonly overwhelmed by the tumor and may be largely unresponsive to active stimulation, it would seem appropriate to treat cancer patients with antibodies produced in another host who has been cured of an antigenically similar tumor.

The role of humoral antibodies in immunotherapy remains controversial and their widespread use in treating cancer patients must await a better understanding of their role in tumor immunity. Though certain types of humoral antibodies are demonstrably cytotoxic for tumor cells in culture and cytophilic for lymphocytes and macrophages, some serum components (blocking factors) may enhance tumor growth.[11] However, it appears that the time-course relationship for administration of humoral antibodies is critical, with markedly different effects from administration at differing times.

Because the cellular immune system is believed to be predominant in the immune response to tumor, treatment with sensitized lymphocytes would appear to be an ideal method of immunotherapy. Difficulty in finding cured donors with matching tumor and transplantation antigens to the recipient host has severely limited the usefulness of this method.

However, other very interesting approaches to immunotherapy are emerging. For instance, Moore and Gerner have grown a patient's lymphocytes in culture to increase their number, and then reinfused them into the same patient.[12] Other investigators have removed lymphocytes from cancer patients and attempted to increase the effectiveness of the lymphocytes by stimulating them with phytohemagglutinin or tumor antigens before reinfusing them into the donor patient.

Methods of transferring informational molecules from sensitized lymphocytes have also been described. In 1955, Lawrence[13] described the cell-free transfer of delayed hypersensitivity, using a low molecular weight substance termed transfer factor.

Though preparation techniques vary, transfer factor may be produced by lysing sensitized lymphocytes and extracting those substances with a molecular weight between 15,000 - 20,000. Such an extract is free of larger molecules, such as hepatitis virus and transplantation antigens. Administration of transfer factor will result in a nonreactive recipient developing the donor's skin test reactivity within 24-72 hours, and retaining that reactivity for at least two years.[14] Transfer factor is capable of transferring cellular immunity to skin tests, tuberculosis and a variety of antigens, though it does not appear to alter the humoral system. Even though transfer factor has been useful in the treatment of some types of immune deficiency disease, its effectiveness in treating human cancers has been limited.

Another substance capable of transferring cellular immunity was described by Alexander *et al*[15] in 1967, involving the transfer of "immune" RNA. "Immune" RNA may be derived either from lymphocytes of a cured human donor or a specifically immunized animal, and may be administered parenterally or by incubation with a patient's lymphocytes *in vitro* before reinfusing them. The use of "immune" RNA in cancer therapy has as yet been too limited to establish its future efficacy.

Another interesting way in which the immune system may be utilized in treating cancer is to use the antibodies merely as specific carrying agents. In such a system, chemotherapeutic agents or radioactive isotopes are attached to tumor specific antibodies, thus delivering them specifically to tumor cells. In addition, scanning for isotope concentrations might provide an effective means of localizing aggregates of tumor cells.

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X-RAY OF THE MONTH

PNEUMOCEPHALUS FROM PARANASAL SINUS CARCINOMA

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Boston, Massachusetts

PATIENT

A 49-year-old afebrile male presented with headache and recent behavioral changes. Past history indicated he had received 3000 rads of Cobalt 60 to the right submandibular gland in 1971, followed by right radical neck dissection. Recurrent tumor infiltrating the right frontoethmoid, sphenoid and maxillary sinuses required additional radiotherapy. A persistent cerebrospinal fluid leak developed in 1973 and required repair through a bifrontal craniotomy. The dural specimen contained undifferentiated carcinoma.

RADIOGRAPHS

Skull films taken in the upright (Fig. 1A) and supine positions (Fig. 1B) demonstrated an air-fluid level in the left frontal area. A CT scan without contrast (Fig. 1C) confirmed the presence of a cavity in the left frontal lobe. The central white area in the cavity represents computer "overshoot" artifact, seen when there is a considerable difference in absorption values of adjacent structures.

DIAGNOSIS

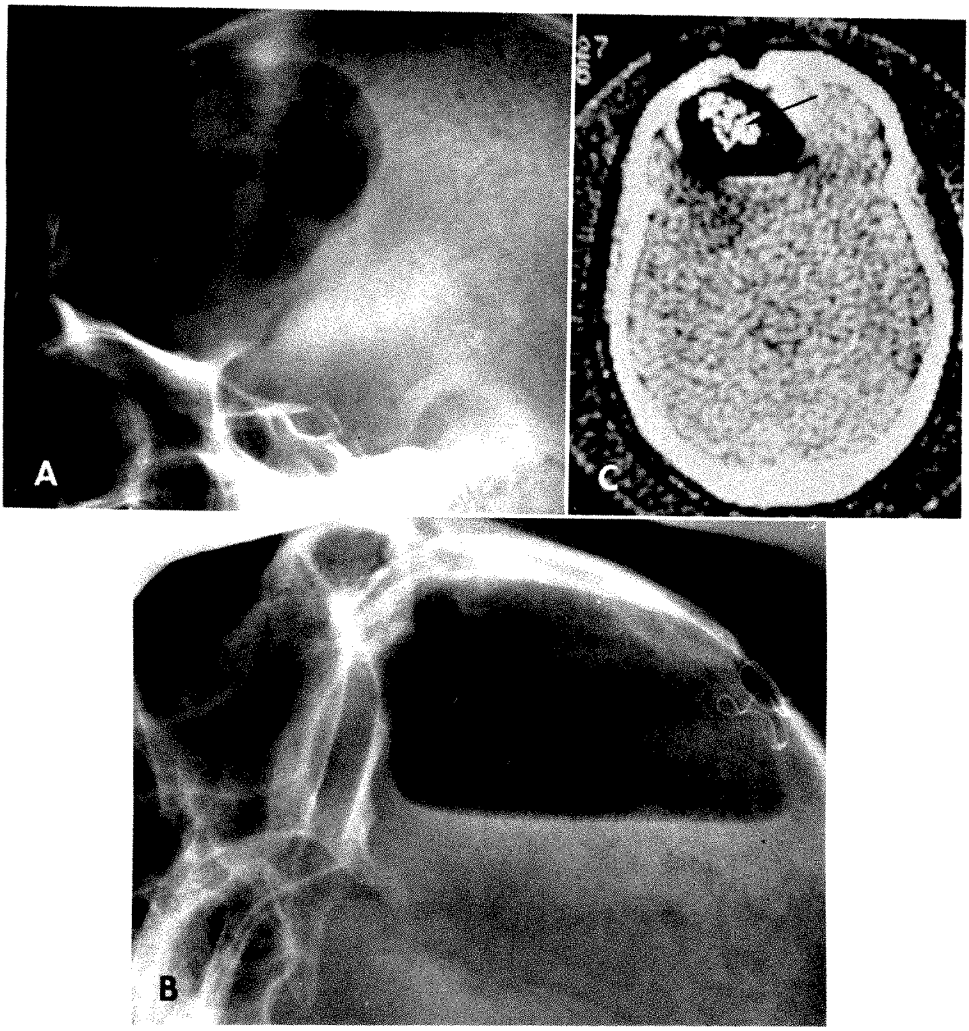
At surgery a fibrotic capsule which was densely adherent to adjacent brain was found surrounding a large air- and fluid-filled cavity in the left frontal lobe. Although the capsule could not be removed, a 2 to 3 mm tract was excised and the cribriform plate defect repaired.

DISCUSSION

Pneumocephalus as a result of nasopharyngeal or paranasal sinus tumor eroding the base of the skull is a rare event.[1] Skull fractures and penetrating wounds remain the most common causes of pneumocephalus. Rhinorrhea or otorrhea provide useful clinical diagnostic information for this complication. Chronic ear, sinus and chest infections from gas-forming organisms (clostridia perfrigens, anaerobic streptococci, diphtheria bacillus, pneumococci and actinomyces) as well as intracranial foreign bodies are the common sources.[2] Pneumocephalus associated with chromophobe adenoma,[3] frontal osteomas and mucoceles,[4] and epidermoids has been reported.

The present case demonstrates the formation of a tension pneumocephalus. Intracranial gas may be epidural, subdural, subarachnoid, intraventricular or parenchymal in location. Since it is occasionally difficult to precisely locate gas with skull films alone, the CT scan is employed to aid preoperative evaluation.

From the Departments of Radiology, Massachusetts General Hospital and Massachusetts Eye and Ear Infirmary, Boston, Massachusetts.



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BOOK REVIEWS

Handbook of Sensory Physiology (Volume V/2) Auditory System

Edited by *W. D. Keidel* and *W. D. Neff*. Hard cover, 210 illustrations, referenced, indexed, 527 pp, 1975. Springer-Verlag, New York. Price $95.20

The eleven chapters of this second volume can be classed into three groups: 1) Neurophysiology (1-5); 2) Behavioral Studies (6-9); and 3) Psychophysics (9-11).

The four chapters dealing with the *afferent* system in an ascending order (E. F. Evans; J. M. Goldberg; S. D. Erulkar; M. H. Goldstein & M. Abeles) will be reviewed together.

At the level of the cochlear nerve (Evans), there is no interaction between fibers. Each may be considered a separate channel. Its activity can be understood in terms of the input, *i.e.*, basically in terms of cochlear mechanics. Therefore, the contemporary technique of wholly computerized experimentation (where the computer generates the input signal and registers and collates the responses as well) has yielded precise and impressive results. The experimenter knows in principle what kind of responses he may expect and can program his computer accordingly. This is a relatively simple system, and our concept of its function is well-advanced.

Starting at the cochlear nuclei (Evans) things become more complicated. There are cells with integrative functions. Their outputs are currently not clearly definable, since they are related to an unknown multiplicity of inputs. Only a portion of the outputs are "primary-like." There is a variety of new patterns. Some cells even appear to change output patterns with time for no apparent reasons. (The level of anesthesia is but one of them.)

The functions of the pontine nuclei (Goldberg) that are involved in binaural interactions obey once more relatively simple rules. (Binary systems are quite accessible to analysis.) At the inferior colliculus (Erulkar), structure and function become definitely complex. Even the destination of some outgoing connections is still under dispute. At the cortical level (Goldstein & Abeles), activity of many units does not depend on the input alone, but also on the immediate past history of the unit, *i.e.*, on what is being "anticipated." Some 20% of the units, however, have no definable input/output function at all, testifying perhaps to the inherent "plasticity" of the CNS.

Our current predicament, *i.e.*, that we know and understand less and less the higher up we go in the CNS, may be traced to two related reasons: 1) The CNS employs *parallel* processing, and interactions between units lying in parallel to one another becomes more complex the higher the level. 2) Present-day microelectrode techniques do not permit *simultaneous* recording from adjacent units that might respond to the same signal in a different manner. This whole situation may not be alleviated until some machinery is developed that uses parallel processing of the kind employed by the CNS. Then, we will have models, hopefully including mathematical paradigms, to aid us in comprehending CNS functions. It is common experience that our understanding of physiological functions is yearly facilitated by the availability of man-made machinery that is capable of serving as a model in this regard.

Principally the same difficulties exist with regard to the *efferent* system (Chap. 5, J. E. Desmedt). In contrast to its higher-level extensions, only the function of the (peripheral) olivocochlear bundle is reasonably well understood, at least in anesthetized preparations. It appears that, finally, the functions of the system in unanesthetized, unrestricted animals are being unraveled: improvements of signal discrimination in noise and of frequency discrimination.

Chapter 6 (R. A. Butler) deals with two prominent functions of external and middle ears: those having to do with directional hearing and the effects of the middle-ear muscle reflexes on loudness.

Chapter 7 (G. Bredberg & I. M. Hunter-Duvar) discusses an important topic, *i.e.*, the correlation between behavioral testing and histological findings. The relation is still far from being clear, despite all past efforts in this regard. This chapter lists some of the difficulties and sources of error that still exist.

Chapter 8 (W. D. Neff *et al*) takes up cortical functions as seen from the behavioral viewpoint, a field in which the senior author pioneered some 25 years ago. The significance of the cortex for auditory localization and for the assessment of temporal auditory patterns (speech!) are being stressed.

Chapter 9 (E. Zwicker) represents an updating of classical Psychophysics in the tradition of the late S. S. Stevens from Masking, Critical Bands, *etc.*, up to Non-linear Distortions.

Chapter 10 (L. A. Jeffress) describes the psychophysical aspects of sound localization to which its author contributed very substantially himself.

Chapter 11 (D. M. Green and W. A. Yost), finally, reviews, on the basis of psychophysical data, the methods of binaural analysis that lead to improvements in performance, things that generally go under the heading of Masking Level Differences (MLD).

This very condensed synopsis can hardly do justice to the content of this volume. Since all authors were obviously selected on the basis of demonstrated expertise on their assigned topics, the level of presentation is uniformly high. There are no "weak" chapters. This reviewer's slight preference for the chapters by Evans, Goldberg, Bredberg and Hunter-Duvar, and Zwicker, may reflect his own interests more than anything else.

One small item of critique: Many nonphysiologist readers might have benefited from a brief anatomical summary with a few representative figures from Chapters 9 and 11 of the preceding volume at the very beginning of this one. Not everyone needing a quick reference will have the complete set on his own bookshelf.

Taken as a whole, this volume, like the first one, will, for years to come, remain the standard in the field, both for physiologists and psychologists actively working in the field, and for physicians who are seeking an updating of their knowledge from authoritative sources.

JUERGEN TONNDORF, MD

Cerebral Dural Sinuses and Their Tributaries

By *Jefferson Browder* and *Harry A. Kaplan*. Hard cover, 66 illustrations, indexed, referenced, 120 pp, 1976. Charles C. Thomas, Springfield, IL. Price $14.75

This 120-page monograph based upon 950 dissected cerebral dural sinus specimens is of value to both anatomists and clinicians involved with the neurosciences. The complex embryology of the dural sinus development is presented by the authors in a clear and concise manner with accompanying illustrations of 12-80 crown-rump length embryos to complement the text. These embryonic studies clarify to the reader why so many anatomical aberrations of the dural sinuses occur, as well as the fundamentally different venous drainage systems of the scalp, diploe of the cranium, epidural and intracerebral veins.

The authors in subsequent chapters discuss in detail the macro- and microanatomy of the sagittal sinus, confluence of sinuses (torcular Herophili), transverse sinuses, occipital and marginal sinuses, the cavernous sinuses and their major connections, and the deep sinuses (straight sinus, vein of Galen, inferior sagittal sinuses). Several anatomical misconceptions are clarified, such as the failure to substantiate evidence of veins traversing the foramen cecum to connect the anterior sagittal sinus with the veins of the upper nasal cavities. Of particular interest is the authors' developmental and anatomical study of the lateral lacunae with their granulations of arachnoid tissue. The anatomical variants of the sinuses are of particular importance for the clinician concerned with surgery that may potentially compromise patency of the dural sinuses.

The monograph contains 66 illustrations which complement and enlarge the text, and is well-referenced to give the interested reader additional detailed information of these important anatomical structures. It is a valuable and practical addition to the library for both the clinician and anatomist concerned with the neurosciences.

JOHN VAN GILDER, MD

Genetic and Metabolic Deafness

By *Bruce W. Konigsmark* and *Robert J. Gorlin*. Hard cover, illustrated, referenced, indexed by author and subject, 419 pp, 1976. W. B. Saunders Co., Philadelphia, PA 19105. Price: US $32.50; Canada $33.50

The Causes of Profound Deafness in Childhood

By *George R. Fraser*. Hard cover, referenced, indexed, 410 pp, 1976. The Johns Hopkins University Press, Baltimore, MD, 21218. Price $22.50

These two books warrant joint review since they share a common aim, namely, to focus more attention on the causes of deafness with emphasis on those that can be properly classified as hereditary although other causes are also treated. The aims of both volumes are admirably achieved and their differing approaches to the subject in no way argue for a preferred method. Rather they complement each other in illuminating a complex subject that merits the best scientific and professional interest that we have to offer.

The book by Konigsmark, working at Johns Hopkins and Temple University, and Gorlin, from the University of Minnesota, is a scholarly comprehensive compendium of information on genetic and metabolic deafness. Following a general chapter on genetic hearing loss are chapters devoted to genetic hearing loss with no associated abnormalities, with external ear abnormalities (*e.g.*, thickened ear lobes and incudostapedial abnormalities), with eye disease (*e.g.*, retinitis pigmentosa), with musculoskeletal disease (*e.g.*, absence of tibia), with integumentary system disease (*e.g.*, Waardenburg syndrome), with renal disease (*e.g.*, nephritis), with nervous system disease (*e.g.*, ataxia and mental retardation) and with metabolic and other abnormalities (*e.g.*, goiter). The exposition of each disorder, copiously and clearly illustrated, is succinctly organized under clinical, laboratory and other findings, pathology, heredity, diagnosis, prognosis and treatment.

The book by Fraser of the Faculty of Medicine, Memorial University, St. John's, Newfoundland, draws its content from a survey conducted from 1958 to 1967 of 3535 deaf individuals (1848 males, 1687 females, about 20% adults) in the British Isles (including the Republic of Eire) and South Australia. Dr. Fraser's experience in such studies is amply documented by his book, *The Causes of Blindness in Childhood* (Johns Hopkins Press, 1967), coauthored with A. I. Friedmann.

The method involved in most instances was a general clinical examination, inspection of face and skull, palpation of the thyroid gland, ophthalmoscopy, medical and family history and audiometric records where available. The chapters are organized around deafness determined by Mendelian inheritance, deafness as part of nonMendelian malformation syndromes, deafness due to acquired causes, the etiology of deafness of apparently "unknown" cause, and an attempt at synthesis including attention to risk figures and genetic counseling. The author has done very well what he states in his own words "to construct balance sheets of the etiological entities contributing to the causation of profound childhood deafness and to gauge their approximate numerical significance" — this despite difficulties such as confusion that arises between acquired and genetic determination.

These books should contribute to and stimulate needed activity in the further definition of genetically determined deafness through linkage and biochemical investigations. Implicit throughout both books is the recognition that whoever assumes the responsibility for genetic diagnosis needs to be familiar with the characteristics of known syndromes and their significance for management. This information enlightens us as to the level of confidence with which we can now diagnose and counsel about genetic matters. Of course, effective counseling recognizes the requirement of mature sensitivity to the ethical, moral and psychological factors involved in the delicate process of advising people about family planning.

Konigsmark (whose untimely death in 1973 at age 45 was a grievous loss to the field), Gorlin and Fraser have greatly enhanced our understanding of the etiology and pathology of deafness and, in so doing, encourage us to look forward to improved efficacy of management.

S. Richard Silverman, PhD

Disorders of Auditory Function II

Edited by *S. D. G. Stephens*. Hard cover, illustrated, indexed, 311 pp, 1976. Academic Press, Inc., London, England. Price $21

These proceedings of the British Society of Audiology from its July 1975 conference is divided into five sections: noise-induced hearing loss, electrophysiologic measures, pediatric audiology, neuro-otology, and hearing aids. Each section has a central theme, but the four to eight separate papers within each section cover a wide range around that theme. For example, the section on neuro-otology includes: "The investigation of sensorineural hearing loss as exemplified by ethacrynic acid ototoxicity," "The use of electronystagmography in neuro-otological diagnosis," "Signal analysis of neuro-otological measurements," "Auditory temporal summation in patients with central nervous system lesions," and "The diagnostic value of tonal tests in peripheral and central auditory lesions." The papers are concise, clearly presented, and adequately illustrated. Although the majority of the authors are from the United Kingdom, some distinguished guests from other parts of Europe also contributed to these proceedings.

Robert Goldstein, PhD

Hearing Aid Assessment and Use in Audiologic Habilitation

Edited by *W. R. Hodgson* and *P. H. Skinner*. Hard cover, indexed, 288 pp, 1977. The Williams and Wilkins Co., Baltimore, MD. Price $19.15.

This is a good introductory text book for students of audiology, and other professionals interested in this field. Compared to several books on the same subject that have appeared recently, this one has more unity and balance of quality within chapters. The chapter on "Physical Characteristics of Hearing Aids" is very helpful in the understanding of electronic concepts for the uninitiated.

The authors are not afraid to make repeated emphasis on a subject which has often been ignored: "Saturation Sound Pressure Level should be controlled to minimize a potential risk of producing additional hearing loss as a result of overexposure to intense stimuli" (p 112), and "while neither temporary nor permanent threshold shifts from hearing aid use appear to be common phenomena, there is evidence that the utilization of wearable amplification without regard to Maximum Power Output can be traumatic in selected cases" (p 160).

The addition of study-guides or questions would have been welcome. Furthermore, debatable issues (such as the value of binaural fittings) should be clearly identified as subject to discussion. All in all, I find this book a worthwhile addition to our libraries.

David P. Pascoe, PhD

Monoamine Oxidase and Its Inhibition

CIBA Foundation Symposium 39, Iserier-Excerpta-Medica, North Holland. Hard cover, illustrated, referenced, indexed, 415 pp, 1976. American Elsevier Publishing Co., Inc., 52 Vanderbilt Ave., New York 10017.

This book includes the proceedings of a CIBA Foundation Symposium on Monoamine Oxidase and its Inhibition, held in honor of Mary Hare-Bernheim who first described the presence of monoamine oxidase in tissue. The book is composed of 17 papers, each one of which includes an abstract and on the whole is lucid and well-referenced. The authors are noted for their contributions to the field of monoamine oxidase. All papers are followed by a discussion section which is one of the most thorough this reviewer has encountered.

The introductory remarks by S. Kety are followed by discussion of the controversial question of whether the multiplicity of monoamine oxidase preparation is apparent only because of preparative procedures (K. F. Tipton, M. D. Houslay and T. J. Mantle). The evidence for and the nature of multiple forms of monoamine oxidases could have been more thoroughly covered at the symposium but in this fast expanding area more questions have been raised than the answers provided during the last 24 months since this symposium was held. The next three chapters cover structure of the site in inhibited enzyme, the action of some of the monoamine oxidase inhibitors and transformation of monoamine oxidases. T. L. Sourkes and K. Missala discuss the nutritional requirements for amine metabolism. The regulatory role of monoamine oxidases in neuroendocrine function and dopamine metabolism in the central nervous system has been clearly emphasized. These and other physiological and pharmacological aspects of oxidative deamination of monoamines and its inhibition is discussed by M. Youdim and M. Holzbauer; J. Knoll; N. Neff and J. Fuentes; and U-Trendelenburg, K. Graefe and M. Henseling. Behavioral and psychopharmacological responses to monoamine oxidase inhibitors are covered by A. Green and M. Youdim; and L. Montre, A. Delini-Stula and P. Waldmeir. D. F. Sharman discusses the intra- and extraneuronal metabolism of monoamines. Section on clinical aspects of monoamine oxidase inhibition and its role in psychiatry includes five papers contributed by C. Pare; M. Roth and T. Kerr; M. Sandler; D. L. Murphy; and I. Brockington, T. Crow, E. Johnstone and F. Owen. The book ends with a general discussion, standardization of assay techniques and concluding remarks by S. Kety. The two appendices deal with the assay methods for monoamine oxidase and techniques for isolation of human platelets. These are well presented and include sufficient description to be very useful for interested researchers.

This is a valuable book for clinicians and basic scientists. Essentially all of the important areas in the field of monoamine oxidase have been covered. The papers are logically assembled. I believe it will be frequently used by beginning students and established investigators in pharmacology, biochemistry, physiology and psychiatry.

Ranbir K. Bhatnagar, PhD

Acoustic Impedance and Admittance: The Measure of Middle Ear Function

By *Alan Feldman* and *Laura Wilbur*. Hard cover, indexed, illustrated, 383 pp, 1977. Williams & Wilkins Co., Baltimore, MD 21202. Price $23.00

There are two groups of audiologists in this country who are popularizing the merits of measuring the acoustic impedance of the middle ear. By far, the largest and most effective group is led by Drs. James Jerger and Jerry Northern who, along with many other enthusiastic investigators, educators, and clinicians, are promoting the use of the electroacoustic impedance bridge. In their *Handbook of Clinical Impedance Audiometry*, edited by Dr. Jerger and published in 1975, the concepts of acoustic impedance and compliance of the middle ear are explained in relation to the electroacoustic impedance bridge.

Now the opposing group has published their reference book. Drs. Feldman and Wilbur have been the leading proponents of the use of the otoadmittance meter to separate and measure the complex components of acoustic admittance (susceptance and conductance). With a number of steadfast and erudite followers, they contend that *impedance audiometry* is a misnomer since 1) the instruments are actually testing *admittance* or the ease of energy flow, rather than the difficulty of the flow of energy (impedance) encountered at the tympanic membrane, and 2) the measurements obtained are not audiometry. These differences in methodology and terminology, as stated by Drs. Feldman and Wilbur in the introductory chapter, "have tended to fractionate and confuse the professional who enters the arena with a minimal background knowledge." In an effort to clarify these differences and simplify the concepts, the authors have attempted to present the information in a relatively impartial manner. However, due to the lack of uniform standards for instrumentation and for reporting measurements, the subject still remains confusing to all but serious students of the field.

Nevertheless, the book for the most part provides an important reference for those health professionals interested in the measurement of impedance (or admittance) of the middle ear. Drs. Feldman and Wilbur, either together or individually, have written 5 of the 14 chapters. For the remainder they have been successful in obtaining contributions from some of the leading authorities on the subject. About half of the chapters, the more clinically oriented, will be of interest to audiologists and otolaryngologists, while the more technical chapters will primarily be of interest to audiologists. Of particular merit are the chapters written by Eric Borg, MD, PhD (Dynamic Characteristcs of the Intra-Aural Muscle Reflex) and jointly by Karel J. Van Camp, ScD and Wouter L. Creten, ScD (Prinicples of Acoustic Impedance and Admittance). These chapters, though technical in content, present a unique, concise, and relatively simplified discussion of rather sophisticated material. The chapters devoted to clinical testing are presented well and will be of help to the practitioner.

One or two of the chapters could have been deleted as they are essentially identical in content with material presented in other recent texts. The chapters on anatomy and physiology of the middle ear, although written well, are too superficial to be of interest to either audiologists or otolaryngologists. The chapter "Pathologies and Their Effect on Middle Ear Function" will be of interest to those who know and respect the author, Knut Terkildson, MD, but for readers other than the beginning student the information is too basic to be of interest. On the whole, however, the book is an excellent contribution to the field and is a worthwhile reference addition to the libraries of those professionals concerned with the measurements of middle ear function, whether their reference points be impedance or admittance.

Charles D. Bluestone, MD

ABSTRACTS FROM
NATIONAL AND INTERNATIONAL JOURNALS

Microwave Treatment for Sudden Deafness

Kawamoto H, Naito T: Med J Osaka Univ (In English) 27:77-86, 1976

Patients with sudden deafness were treated with irradiation by a 20-30 watt microwave apparatus at a frequency of 2,450 mHz from outside the auricle on the affected side toward the inner ear for 15 minutes, once or twice a day, over a period of ten days.

The microwave irradiation improved blood flow in vertebral, basilar, anterior inferior cerebellar and labyrinthine arteries, and related arterioles and veins which contribute to the function of the inner ear.

Statistical comparison was made between 57 cases in group A which were treated with combined therapy (microwave and drugs) and 91 cases in group B which were treated with drugs only. The rate of complete cure and remarkable recovery was statistically higher in group A than in group B, when the treatment was started within two weeks after the onset of sudden deafness. There were two completely cured patients in group A whose treatments were initiated as late as the 28th and 51st day after the onset of the disease.

Microwave treatment produced excellent effects when care was taken to prevent overheating. The simplicity of this method, its low cost and lack of discomfort to the patient are definite merits of this therapeutic procedure. No serious side effects were found with microwave treatment.

M. Igarashi

Thyroid Cancer Occurring as a Late Consequence of Head and Neck Irradiation

Favus MJ, Schneider AB, Stachura ME, et al: N Engl J Med 294:1019-1025, 1976

A prospective epidemiologic study was designed to identify a correlation between head and neck irradiation for benign disease and latent thyroid carcinoma. The authors examined 1,056 patients who received radiation therapy in the 1940's and 1950's for infectious and inflammatory diseases of the nasopharynx and tonsils. Thyroid nodules were palpated in 16.5% of these patients. Pertechnetate thyroid imaging revealed nonpalpable disease in an additional 10.7% of the subjects. Operative procedures were performed on 196 (72%) of the 270 abnormal patients. Thyroid carcinoma was found in 33% of the operated group. All of the carcinomas were well-differentiated with no metastatic lesions.

It was concluded that a 9% prevalence of thyroid cancer exists more than 30 years following radiation therapy to the head and neck. Other significant findings included: the absence of palpable disease with a positive scintigram should not be a deterrent to proceed with surgery; the frequency of carcinoma in multinodular glands was the same as in single thyroid nodules in this population; nodular thyroid disease was more prevalent in women, but the existence of thyroid carcinoma was not dependent on sex; and finally the age of initial exposure and the dosage of radiation were not found to be significant carcinogenic variables.

The magnitude of this problem is compounded by the fact that many of these people had no knowledge of their radiation exposure.

B. Gantz

Electron Beam Therapy in Head and Neck Tumors

Tobin DA, Hall W, Scott RM: Am J Roentgenol Radium Ther Nucl Med 126:1251-1255, 1976

The authors have analyzed their experience with 153 cases of head and neck neoplasms using electron beam therapy. These lesions involved alveolar ridge, floor of mouth, buccal mucosa, retromolar trigone, tonsil, parotid, and tongue and pharynx. All patients were treated for cure with doses varying from 5,500 rads in 30 days to 7,000 rads in 68 days. The reasons for considering electron beam therapy include its skin sparing effects, rapid dose buildup and fall off, and preservation of tissues in normal tissue contralateral to the beam.

Results of this series show 79 survivors at two years. The best results are in floor of mouth with 66% survivors at two years. Worst results are in pharynx with 12% two-year survival. Except for alveolar ridges (23%), the remainder of the two-year survivals figured are between 50-60%.

Conclusions to be gained include a poor response in tumors near the midline of head or neck areas. Although patient acceptance seemed to be good, erythemia, dry desquamation, and mucocytes were judged the same as photon therapy. Some cases had attempts at surgical salvage, and surgeons reported the tissue handling characteristics to be similar to photon treated tissues. The authors state that complications "appear diminished," survival "comparable," and quality of life improved with respect to photon therapy. Little documentation of this, however, is given.

D. Leopold

Recurrent Staphylococcal Abscesses Associated with Defective Neutrophil Chemotaxis and Allergic Rhinitis

Hill HR, Williams PB, Krueger GG, et al: Ann Intern Med 85:39, 1976

Four patients are discussed, with histories of recurrent staphylococcal furunculosis and deep abscess formation which typically followed episodes of allergic rhinitis. A marked defect in neutrophil granulocyte chemotaxis was found to be present when the patients were symptomatic with rhinitis and abscess, but this function returned to normal during the symptom-free interval periods. Neutrophil random migration, phagocytosis, bactericidal activity, lymphocyte T-cell populations and serum concentrations of IgA, IgG, IgM and IgE were normal. Recurrent abscesses due to defective neutrophil granulocyte chemotaxis have been demonstrated in atopic disease, such as eczema and urticaria, in association with an elevated serum IgE. This study presents cases of intermittently defective neutrophil function associated with only nasal allergic symptoms and normal IgE.

C. Campbell

Competent Cellular Immunity in Allergic Rhinitis Patients with Elevated IgE

Yocum MW, Strong DM, Lakin JD: J Allergy Clin Immunol 57:384-388, 1976

An inverse relationship between serum IgE levels and cell-mediated immunity has been suggested by clinical observations and by experimental findings in rodents. The present study was designed to test this hypothesis by studying cell-mediated immunity in allergic rhinitis patients having elevated serum IgE levels.

The mean serum IgE level in allergic rhinitis patients was 1,421 IU/ml, compared to 101 IU/ml in the control group. Evaluation of cell-mediated immunity included skin testing for delayed hypersensitivity (Candida. Trichophyton, mumps, tetanus-diphtheria toxoids and streptokinase-streptodornase) lymphocyte blastogenesis (antigen-and mitogen-stimulated) and erythrocyte rosette assays. No abnormalities in these tests of cell-mediated immunity were found in the allergic rhinitis group.

Thus, this study demonstrates normal cell-mediated immunity in atopic patients and fails to support the initial hypothesis.

H. Richerson

Nasopharyngeal Carcinoma in Children

Fernandez CH, Cangir A, Samaan NA, et al: Cancer 37:2787-2791, 1976

In a retrospective study from the M. D. Anderson Hospital, the authors report their experience using irradiation to treat ten children (ages 10-15 years) with nasopharyngeal lymphoepithelioma. Clinical presentation included cervical adenopathy (six patients), nasal obstruction (two patients), and back pain (one patient). Primary sites were treated with 60Co irradiation ranging from 4300 rads/31 d to 6500 rads/33 d with modification of fields according to local extension. An additional 5000-6000 rads in 5-6 weeks was used for treatment of neck nodes. Three of the children died of metastases. Seven of the children are alive; six are free of disease with survival time ranging from 2½ to 14 years (mean survival of 9 years). For eight of ten patients who had five-year follow-up, the five-year survival rate was 62.5%. Five of the ten children experienced manageable postradiation endocrine complications related to hypopituitarism and/or hypothyroidism.

The article deals with an unusual tumor of childhood, presents a reasonable method of therapy usually employed in treating adult nasopharyngeal carcinoma, and emphasizes postradiation endocrine complications.

E. Kraus

Five-Year Survival Following Cyrosurgery for Oral Cancer

Gage AA: Arch Surg 111:990-994, 1976

The author presents a review of 60 patients over five years in which cryosurgery was used as the primary mode of treatment for head and neck cancer. To use cryosurgery on squamous carcinoma, he cites the following criteria: the disease must be localized; the lesions must be small to moderate size, preferably overlying bone; there should be no cervical lymphadenopathy; and the patient should be a high surgical risk.

In his survey, his patients were selected due to their severe associated medical diseases, and over five years he found that 25 of 60 were still alive, nine deaths being associated with persistent primary cancer and ten with metastatic tumor present, but none in the treated area.

He emphasizes that cryosurgery allows good wound healing and pain relief because of the effect on sensory nerves and, importantly, leaves other modes of treatment available. Usually, failure of cryosurgery is evident within a month.

B. Costello

PROGRAMS

AMERICAN BRONCHO-ESOPHAGOLOGICAL ASSOCIATION
PRELIMINARY SCIENTIFIC PROGRAM
PALM BEACH, FLORIDA

APRIL 24-25, 1978

Chevalier Jackson Lecturer, George Berci, MD

Unsuspected Foreign Bodies of the Aerodigestive Tract. William Banks, MD, William P. Potsic, MD

Gastritis Secondary to the Ingestion of Corrosive Agents. John J. Welsh, MD

Insufflation Esophagoscopy. Enie Th. Edens, MD

Aortic Arch Anomalies in Adult Disorders of Deglutition. Lee D. Rowe, MD, Louis D. Lowry, MD, W. M. Keane, MD, Manoucher Fallenjad, MD

The Case for Pneumatic Dilatation in Achalasia. Terence W. O'Connor, MBBS, FRCS, Dionisis C. Flores, MD, Henry J. Heimlich, MD, FACS

Functional Diseases of the Esophagus: The Role of Endoscopy. Najunda Swaney, MD, John Rayl, MD

Traumatically Acquired Conditioned Dysphagia in Children. William De Scipio

New Instruments — A New Endotracheal Tube for Laser Surgery of the Larynx. Martin L. Norton, MSPH, MD, Paul DeVos, MD

Mucociliary Transport. Marvin A. Sachner

Ultra-Violet-Fluorescence Bronchoscopy in Early Detection of Bronchogenic Carcinoma. D. Hurzeler, MD

Sputum Cytology Testing in the Diagnosis of Upper Respiratory Tract Cancer. H. B. Neel, III, MD, L. B. Woolner, MD, D. R. Sanderson, MD

The Effect of Topical Anesthetics on the Ciliary Activity of a Chicken Tracheal Organ Culture System: A Study Using Total Immersion and Intratracheal Injection. James P. Dudley, MD, J. D. Cherry, MD

Tracheal Tension Characteristics Following Tracheal Resection. Arlen D. Meyers, MD, Harry L. Bishop, MEE

Mediastinoscopy: The Predictive Survival Value in Staging Carcinoma of the Lung. Louis W. Welsh, MD

Hyoid Autograft Repair of Chronic Subglottic Stenosis: Clinical Study. Matthew L. Wong, MD, Bruce W. Jafek, MD, Douglas A. Finnegan, MD

Epiglottitis: A 20-Year Study of Patients Treated with Tracheostomy. Seymour Cohen, MD, Alma Suehiro, MD, John H. Chai, MD, Susan Shackelton, MD

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AMERICAN LARYNGOLOGICAL ASSOCIATION
PRELIMINARY SCIENTIFIC PROGRAM
PALM BEACH, FLORIDA

APRIL 22-23, 1978

Acute Obstructive Laryngitis in Children. Francis W. Davison, MD

Men and Institutions — Otolaryngology in 1878. John F. Daly, MD

Philadelphia's Contribution to Early Laryngology. Charles M. Norris, MD

The Early Chicago Era and Pioneers at Rush Medical School. Stanton A. Friedberg, MD

Otolaryngology and the West. Alden H. Miller, MD

The Fourth Daniel C. Baker, Jr., MD, Memorial Lecture

Energy and the Larynx. B. Raymond Fink, MD

Panel: Diagnosis and Treatment of Vascular Tumors of the Head and Neck. Max L. Som, MD, Moderator

Carotic Body Tumors or Chemodectomas. Paul H. Ward, MD

Glomus Jugulare and Glomus Vagale Tumors. Joseph H. Ogura, MD

Juvenile Nasopharyngeal Angiofibroma of the Nasopharynx. Hugh F. Biller, MD

Vascular Anomalies or Hamartomas of the Head and Neck. Don F. Harrison, MD

Hemangiomas of the Head and Neck. Walter P. Work, MD

Modern Methods of Roentgen Diagnosis and Embolization. Hilal Sadek, MD

The Timed Sequence of Laryngeal Anomalies. John A. Tucker, MD, Gabriel F. Tucker, Jr., MD

Subglottic Stenosis in Children. Blair Fearon, MD

Compendium of Rare Diseases of the Larynx in the Pediatric Age Group. Seymour R. Cohen, MD

Treatment of Congenital Choanal Atresia by the Laser. Gerald B. Healy, MD, M. Stuart Strong, MD

Cyclic Infection of Lymphoid Tissue. Joseph L. Goldman, MD

Hypersensitivity Problems in Otolaryngology. Russell I. Williams, MD

Laryngoceles and Laryngeal Cysts: An Historical Review. Lauren D. Holinger, MD, Paul H. Holinger, MD

Randomized Evaluation of Preoperative and Postoperative Radiation Therapy for Supraglottic Carcinoma. James B. Snow, Jr., MD

Immune Competence in Head and Neck Cancer Patients. Philip M. Sprinkle, MD

Thorotrast-Induced Pharyngeal Necrosis. Andrew W. Miglets, MD

Treatment of Radiation-Induced Tissue Injury by Hyperbaric Oxygen. William R. Hudson, MD

Surgical Treatment of Acute Blunt Laryngeal Injuries. Nels R. Olson, MD

Diagnosis of Myasthenia Gravis of the Larynx. Eugene Rontal, MD

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AMERICAN OTOLOGICAL SOCIETY, INC.
PRELIMINARY SCIENTIFIC PROGRAM
PALM BEACH, FLORIDA

APRIL 23-24, 1978

Hypercholesterolaemia and Other Vascular Alterations as a Cause of Auditory Dysfunction (Experimental Studies). Tetsuo Morizono, MD, Michael M. Paparella, MD

Sudden or Fluctuant Hearing Loss and Vertigo in Children Due to Perilymphatic Fistula. Charles D. Bluestone, MD, K. M. Grundfast, MD, T. J. Reichert, MD

Tinnitus: Treatment with Auditory Stimulation. Jack L. Pulec, MD, Susan F. Hodell, MA

Responses to Bithermal Caloric Stimulation and Harmonic Acceleration in the Vestibular Patient. James W. Wolfe, PhD, Edward J. Engelken, MS, James E. Olson, MD

Otosclerosis: Vestibular Symptoms and Sensorineural Hearing Loss. D. Thane R. Cody, MD, PhD, Hillier L. Baker, Jr., MD

Facial Nerve Repair in the Cerebellopontine Angle. Derald E. Brackmann, MD

Use of Center-of-Force Trajectory Recordings for Screening the Integrity of the Human Vestibulospinal System. F. Owen Black, MD, Conrad Wall III, PhD, Dennis P. O'Leary, PhD

Perilymph Fistulas: Diagnostic Criteria and Therapy. George T. Singleton, MD, Kathryn Nolan Post, MA, Marc S. Karlan, MD

Pinealoma — Selective Hearing Impairment. Scott N. Reger, PhD

Trans-Stapedial Labyrinthectomy: A 15-Year Clinical Analysis. Mendell Robinson, MD

Delayed Endolymphatic Hydrops. Harold F. Schuknecht, MD

Asymmetry of the Internal Auditory Canal without Acoustic Neuroma. Kenneth D. Dolan, MD, Richard W. Babin, MD, Charles G. Jacoby, MD

Cross-Power Spectral Density Analysis of Pursuit Tracking in the Evaluation of Central and Peripheral Vestibular Pathology. James W. Wolfe, PhD, Edward J. Engelken, MS, James E. Olson, MD

Pathology of Chronic Otitis Media and Mastoiditis. Michael M. Paparella, MD, William L. Meyerhoff, MD, C. S. Kim, MD, Sherry Lamey

Clinical Use of Pseudorandom Binary Sequence White Noise in Assessment of the Human Vestibulo-Ocular System. Conrad Wall III, PhD, F. Owen Black, MD, Dennis P. O'Leary, PhD

THE TRIOLOGICAL SOCIETY
PRELIMINARY SCIENTIFIC PROGRAM
PALM BEACH, FLORIDA

APRIL 25-27, 1978

Fifty Years in Otolaryngology. Moses Lurie, MD

Health Economics and Social Choice. Victor R. Fuchs, PhD (By Invitation)

The Early Detection and Treatment of Cancer: Costs and Benefits. Jerry Cromwell, PhD, Paul Gertman, MD (By Invitation)

Benefit Cost-Ratio in Our Search for Cerebellar Pontine Angle Tumors. Ralph Caparosa, MD

Complications of Intranasal Ethmoidectomy: A Review of 1,000 Consecutive Operations (1957-1972). Eugene B. Kern, MD, Harvey M. Freedman, MD (By Invitation)

Care of the Eye in the Paralyzed Face. Mansfield F. W. Smith, MD, Richard L. Goode, MD

Discussion. Arnold M. Cohn, MD, Roger L. Crumley, MD

Tympanoplasty Tubes: Their Use, Abuse, and Cost-Benefit Ratio. B. W. Armstrong, MD, R. B. Armstrong, MD (By Invitation)

Eustachian Tube Function Related to the Outcome of Tympanoplasty in Children. C. D. Bluestone, MD, E. I. Cantekin, PhD, G. S. Douglas, MD, J. D. Donaldson, MD, Q. C. Beery, PhD, S. E. Stool, MD

Radiation Associated Disease, Disease Incidence and Cost Effectiveness of Thirty-Year Follow-Up. Victor L. Schramm, Jr., MD, Robert G. Carroll, MD (By Invitation)

Cellular Immunity in Patients with Epidermoid Cancers of the Head and Neck; Surface Membrane Markers, PHA Stimulation, DNCB Reactivity and the LAI Assay. A. Kukwa, MD, P. Panhausen, MD, C. Croft, MD, B. Borowiecki, MD, E. Emeson, MD (By Invitation)

Interpretation of and Significance of Atypia in Laryngeal Papillomatosis. Cedric A. Quick, MD, L. P. Dehner, MD, Elliot Foucar, MD (By Invitation)

Chemotherapy — Its Known Value in 1978. Emil T. Frei III, MD (By Invitation)

Symposium — Adjuvant Cancer Therapy of Head and Neck Tumors. Introduction — John Conley, MD, Moderator

Preoperative X-Ray Treatment with Presumptive Goals and 1978 Attainments. Douglas Bryce, MD

Postoperative X-Ray Therapy with Presumptive Goals and 1978 Attainments. Robert M. Byers, MD (By Invitation)

Preoperative and Postoperative Chemotherapy with Presumptive Goals and 1978 Attainments. John M. Kirkwood, MD (By Invitation)

Increased Survivorship with Surgery vs. Combined Therapy with Preoperative Irradiation. David E. Schuller, MD, W. Fred McGuirt, MD, Charles J. Krause, MD, Brian A. Pflug, MA (By Invitation)

Summation of Symposium Papers. George A. Sisson, MD

Health Care Costs of Laryngeal Surgery. Stanley E. Thawley, MD (By Invitation), Joseph H. Ogura, MD

Effect of Prophylactic Antibiotics in Radical Head and Neck Surgery. Richard L. Goode, MD, Willard E. Fee, Jr., MD, Paul A. Levine, MD (By Invitation)

Discussion. Milton G. Yoder, MAJ, MC, (By Invitation)

Glottic Reconstruction After Near Total Laryngectomy. Harvey M. Tucker, MD, Howard Levine, MD, Benjamin Wood, MD, Robert Katz, MD (By Invitation)

Washington Report. Harry W. McCurdy, MD, The American Council of Otolaryngology

Dogs for the Deaf — Audio-Visual Report. Holliston Junior College, Lenox, Massachusetts Campus

Value of Diagnostic Procedures: A Contemporary Tale of Society and Technology. E. James Potchen, MD (By Invitation)

Symposium — Value and Cost Analysis of Recent Ear Tests. Brian F. McCabe, MD, Moderator, Introductory Remarks

School Audiometry: A New Method to Improve Accuracy. Edward E. Jacobs, MD, William G. Lavelle, MD (By Invitation)

Value and Cost Analysis of Electrocochleography in 1978. Joseph B. Nadol, Jr., MD (By Invitation)

Value and Cost Analysis of ENG in 1978. Wallace Rubin, MD

The Role of Air-Caloric Testing in Preop and Postop Cases of Chronic Otitis Media. William Meyerhoff, MD, Tetsuo Morizono, MD (By Invitation), Michael M. Paparella, MD

Summation. Brian F. McCabe, MD

Symposium — Otologic Surgery Reassessment After 25 Years. Bruce Proctor, MD, Moderator, Introductory Remarks

The Current Status of the Tympanoplasty. Michael E. Glasscock III, MD, Ronald L. Steenerson, MD, C. Gary Jackson, MD (By Invitation)

Otosclerosis Surgery — Reassessment of Its True Value in 1978. Kenneth H. Brookler, MD

Homografts and Ossicular Grafts — Their Value Revisited in 1978. T. Manford McGee, MD

Summation. Bruce Proctor, MD

A 1978 Assessment of Surgical Procedures for Endolymphatic Hydrops. James B. Snow, Jr., MD

Symposium — Cochlear Implant 1978 — Fact or Supposition. Robin P. Michelson, MD, Moderator

Protocol for Determining the Auditory Percepts of Electrical Stimulation of the Cochlea. Robin P. Michelson, MD, Earl Schubert, PhD, Sheila Walsh, MA, Mark White, PhD (By Invitation)

The Histopathology of Intracochlear Electrode Implantation. Robert A. Schindler, MD (By Invitation)

Bilateral Cochlear Implants, Histological Findings in a Pair of Temporal Bones. Lars-Goran Johnsson, MD (By Invitation), William F. House, MD

Summation of Symposium Papers. Francis A. Sooy, MD

63RD ANNUAL

POSTGRADUATE COURSE

HEAD AND NECK ANATOMY
and
CLINICAL OTOLARYNGOLOGY

JULY 10-21, 1978

Indiana University School of Medicine
Indianapolis, Indiana

The oldest, most intensive lecture and laboratory course in anatomy and histopathology of the head and neck in the country. Clinicians and anatomists are teamed for lectures. Laboratory work includes dissections of temporal bone with microscopy.

Useful for preparation prior to board examinations in otolaryngology, plastic and oral surgery. Also a review of current practice for board certified otolaryngologists and residents training in this specialty.

ENROLLMENT LIMITED
Fee: $750
Make reservations soon

For further information write: Raleigh E. Lingeman, MD, Professor and Chairman, Department of Otolaryngology, Indiana University School of Medicine, 1100 West Michigan Street, Indianapolis, Indiana 46202.

≈

YALE UNIVERSITY SCHOOL OF MEDICINE
Otolaryngology Section
Department of Surgery

will present symposium

COMBINED TREATMENT MODALITIES IN CANCER OF THE HEAD AND NECK

MARCH 30-31, 1978

Two-day international symposium on combined therapy for cancer in high risk areas of the head and neck.

Surgical techniques and concepts will be presented by a guest faculty including: Drs. Ettore Bocca, John Conley, Donald F. N. Harrison, Richard Jesse, Max Som and Elliott Strong.

The impact of chemotherapy and immunotherapy on local treatment by surgery or radiation will be discussed by Drs. Joseph Bertino, Paul Chretien, James Fischer and Robert Wittis.

For further details please contact: Office of Graduate and Continuing Education, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06510. Tel. (203) 432-4582.

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POSITION OPENING

DIRECTOR OF THE AUDITORY RESEARCH LABORATORY

University of Pittsburgh School of Medicine
Eye and Ear Hospital of Pittsburgh
Department of Otolaryngology

Direct and stimulate basic science research projects in the auditory system and related areas, and demonstrate potential to attract outside sources of funding; fulfill the educational responsibilities of the University of Pittsburgh and University Health Center Hospitals; supervise the administration and coordination of the Auditory Research Laboratory; possess an M.D. or Ph.D. degree and be recognized nationally and internationally as a leader in Auditory Systems Research.

Contact: F. Owen Black, MD, Eye and Ear Hospital of Pittsburgh, 230 Lothrop Street, Pittsburgh, PA 15213.

An affirmative action/equal opportunity employer.

FIRST INTERNATIONAL COURSE
on
MULTICHANNEL COCHLEAR IMPLANT
PARIS, FRANCE

SEPTEMBER 21-24, 1978

Presided by PROFESSOR PAUL PIALOUX

Conducted by PROFESSOR CLAUDE-HENRI CHOUARD and PROFESSOR PATRICK MACLEOD with help of specialist guest speakers.

Limited to 50 physicians.

Course will consist of theoretical lectures, operations demonstrated by color television and practical demonstrations (with help of monitors) on surgical technics on the temporal bone (microscope Zeiss), phoniatric readaptation, and electronic device.

Preliminary Program: physiology of intensity and frequencies discrimination; speech recognition; surgical anatomy of cochlea; anatomopathological basis; patients selection; implanted and external electronic devices; surgical procedures; phoniatric methods, clinical results.

Registration fees (including luncheons and suppers) $600.

Official languages are English and French (simultaneous translation).

For further details and registration, write: Pr. C.-H. Chouard, Hôpital Saint-Antoine, 184, rue du Faubourg Saint-Antoine, 75012 Paris, France.

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COURSE FUNCTIONAL MICROSURGERY OF THE EAR

JUNE 29 - JULY 8, 1978

PORTMANN FOUNDATION
and
ENT DEPARTMENT, UNIVERSITY OF BORDEAUX II (FRANCE)

Conducted by Professor Michel Portmann, MD, with the participation of Dr. Guy Lacher, and the collaboration of the staff of the ENT Department, University of Bordeaux.

Course includes: Theoretical and practical lectures; Otological operations demonstrated by color television; Laboratory sessions on the temporal bone; Case presentations.

FEE: 2500 French francs

For information and registration write: Secretary of the Course, Clinique Universitaire d'O.R.L., 86, Cours d'Albret, 33000 Bordeaux, France.

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THE DEPARTMENT OF OTORHINOLARYNGOLOGY
and
THE PAGE AND WILLIAM BLACK POST-GRADUATE SCHOOL OF MEDICINE OF THE MOUNT SINAI SCHOOL OF MEDICINE (CUNY)

Announce a Post-Graduate Course
TEMPORAL BONE SURGERY

Under the Direction of
SIMON C. PARISIER, M.D.

MARCH 6-10, 1978
Monday-Friday — 9:00 A.M. to 6:00 P.M.
(5 Sessions)

This intensive five day laboratory course is designed to familiarize otolaryngologists with the various surgical approaches and technics currently in use in the management of diseases of the temporal bone. Fresh cadaver material and operating microscopes will be available.

FEE: $500

This course will be given at the Mount Sinai Medical Center, New York City, New York.

Apply to: Director, The Page and William Black Post-Graduate School of Medicine, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, New York 10029. Tel. (212) 650-6737.

OTOLARYNGOLOGISTS

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To associate with a large and well-established multispecialty group. Excellent salary and benefits which include continuing educational program, paid malpractice, retirement plan, medical and dental coverage, life insurance. Partnership available after two years.

Write and send C.V. to James D. Roorda, MD, 1505 North Edgemont No. 1J, Los Angeles, CA 90027.

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DEPARTMENT OF OTOLARYNGOLOGY
and
EXTENDED PROGRAMS IN MEDICAL EDUCATION
at
UNIVERSITY OF CALIFORNIA
SCHOOL OF MEDICINE
San Francisco
will present a two-day

INTERNATIONAL SYMPOSIUM
LARYNGEAL FUNCTION
AND SURGERY

March 29-30, 1979

Will include normal and abnormal physiology and surgery (techniques, results and complications) of the larynx. Treatment of benign and malignant lesions with conventional, conservation, reconstructive and laser surgical techniques will be presented.

Program is approved for Category 1 credit of the Physician's Recognition Award of the American Medical Association and the California Medical Association.

For further information please contact: Extended Programs in Medical Education, University of California, Room 569-U, San Francisco, CA 94143. Tel. (415) 666-4251.

ADVANCED
ENG SEMINAR and WORKSHOP

APRIL 28-29, 1978

Fee: $150

DISNEY WORLD

Faculty:
Hugh O. Barber, MD
Fredric W. Pullen, II, MD
Constance H. Cabeza, MA

For information contact: Constance L. Cabeza, Hearing, Education and Research Foundation, 309 Mercy Professional Building, 3661 S. Miami Avenue, Miami, FL 33133.

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ANNUAL COURSE
HEAD AND NECK ONCOLOGY
UNIVERSITY OF MICHIGAN

MAY 14-19, 1978

Basic course designed to provide the surgeon with systematic approach to head and neck cancer. Broad range of topics will be covered in didactic presentations and cadaver dissection. Included will be: tumor immunology and virology, clinical and radiographic diagnostic techniques, principles of radiation therapy, dental evaluation and prosthetic management, and special emphasis on principles and techniques of surgical treatment with immediate reconstruction.

Enrollment will be limited

Tuition: $500 — Physicians in practice
$350 — Residents

Tuition fee will include anatomic dissection material and all lunches.

Course is approved for 42.5 units of continuing education credit through the Department of Continuing Education of the University of Michigan.

For further information contact: Charles J. Krause, MD, Professor and Chairman, Department of Otorhinolaryngology, University of Michigan Hospitals, Ann Arbor, MI 48109.

THIRD INTERNATIONAL COURSE
OTO-NEUROSURGERY

MARCH 13-16, 1978

GRENOBLE (France)

Under the direction of: Robert Charachon, MD
Michel Portmann, MD
Jean-Marc Sterkers, MD
Claude Chouard, MD

Guest Faculty: William House, MD
Ugo Fisch, MD

Official languages: French - English

For registration and information write: Pr. R. Charachon, Secrétariat du cours d'oto-neuro-chirurgie, Centre Hospitalier Universitaire de Grenoble B.P. 217 X - 38043 Grenoble Cedex (France).

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MULTISPECIALTY GROUP

Needs

OTOLARYNGOLOGIST

Multispecialty group of 66 physicians needs Otolaryngologist to join one other in practice. Central U.S. Metropolitan community of 350,000. Branch of State Medical School offers teaching opportunities. Excellent hospitals and medical facilities. A state university in city. Good complete school system and educational opportunities.

Please reply: H. Tom Gray, MD, Medical Director, Wichita Clinic, 3244 E. Douglas, Wichita, Kansas 67208 (316) 689-9453.

≈

CURRENT MEDICAL, SURGICAL
and
PHYSIOLOGIC ASPECTS OF RHINOLOGY

MAYO CLINIC COURSE

in cooperation with

AMERICAN RHINOLOGIC SOCIETY

JUNE 1-3, 1978

For preregistration information contact: Clifford F. Lake, MD, or Eugene B. Kern, MD, Mayo Clinic, Rochester, MN 55901. Tel. (507) 282-2511.

NEW YORK UNIVERSITY POSTGRADUATE MEDICAL SCHOOL
and
THE BROOKDALE HOSPITAL MEDICAL CENTER

offer a course in

TYMPANOPLASTY

Five day course in Tympanoplasty will be given under the direction of
ADOLPH WOLFERMAN, MD and CECIL D. GRIMES, JR., MD

at

THE BROOKDALE HOSPITAL MEDICAL CENTER

MAY 8-12, 1978

Tuition: $400

Enrollment limited to eight (8) participants

Participants will observe various tympanoplastic procedures in the operating room and dissect temporal bones in the laboratory under the direction of members of the Attending Staff. Lectures will be illustrated with slides and film.

This Continuing Medical Education offering meets the criteria for 37 credit hours in Category I for the Physician's Recognition Award of the American Medical Association.

Hotel accommodations in mid-Manhattan will be available at reduced rates. Transportation from hotel to hospital and return will be provided.

For application forms and further information: William Mackler, MD, Office of Continuing Education, The Brookdale Hospital Medical Center, Linden Blvd. & Brookdale Plaza, Brooklyn, NY 11212. Tel: (212) 240-5317.

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PEDIATRIC OTOLARYNGOLOGY
(Part I)
MAY 31-JUNE 2, 1978

and

MODERN PEDIATRIC BRONCHOESOPHAGOLOGY (Part II)
JUNE 2-3, 1978

at

Crossgates Inn (Oakland), Pittsburgh, PA

Department of Otolaryngology
Division of Continuing Education
UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE
AND CHILDREN'S HOSPITAL OF PITTSBURGH

Course Directors:
Charles D. Bluestone, MD, Herman Felder, MD,
Jack L. Paradise, MD, Sylvan E. Stool, MD

PART I: PEDIATRIC OTOLARYNGOLOGY is a didactic course designed for Otolaryngologists, Pediatricians and Family Physicians concerned with ear, nose and throat diseases in children. Registration unlimited. FEE: $150 physicians; $75 residents.

PART II: MODERN PEDIATRIC BRONCHOESOPHAGOLOGY will utilize the laboratory to demonstrate the use of the Storz-Hopkins lens system, fiberoptic flexible endoscopy, laser microsurgery and tracheotomy. Registration is limited. Consideration will be given to those registered for PEDIATRIC OTOLARYNGOLOGY which precedes this course. FEE: $200.

FEE for both Parts I and II: $300

To register contact: Division of Continuing Education, University of Pittsburgh School of Medicine, 1022 Scaife Hall, Pittsburgh, PA 15261. (412) 624-2653.

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THE E.A.R. FOUNDATION
Announces Course
WHAT THE OTOLARYNGOLOGIST SHOULD KNOW ABOUT HEARING AIDS
FRIDAY, MARCH 31, 1978
Nashville, Tennessee

Co-Chairmen
Michael E. Glasscock, III, M.D., and
Fred H. Bess, Ph.D.

Partial Faculty Listing:
H. A. Ted Bailey, Jr., M.D.
Fred H. Bess, Ph.D.
Barry A. Freeman, Ph.D.
Michael E. Glasscock, III, M.D.
Richard L. Goode, M.D.
Earl R. Harford, Ph.D.
Kathryn B. Horton, M.S.
James K. Jerger, Ph.D.
E. W. Johnson, Ph.D.
Dan F. Konkle, Ph.D.
Samuel F. Lybarger
Gale W. Miller, M.D.
Wayne O. Olsen, Ph.D.
Mark Ross, Ph.D.
Jay W. Sanders, Ph.D.
Daniel M. Schwartz, Ph.D.
Michael E. Winston, Ph.D.

On August 25, 1977, the F.D.A. drastically changed the hearing aid distribution system in this country. Suddenly the otolaryngologist has, by law, become a part of this delivery system and must be aware of his role. The purpose of this one day course is to familiarize the practicing otolaryngologist with the new federal regulations and give him a working knowledge of how a hearing aid performs and the type of patient who will benefit most from amplification. This is a basic, how-it-is-done course for the busy physician with little prior knowledge of hearing aids.

Tuition: $100

Contact: The E.A.R. Foundation, Baptist Hospital West Building, Nashville, TN 37236. (615) 327-4870.

MICROSURGERY OF THE LARYNX AND VOICE CONSERVATION

BOSTON UNIVERSITY MEDICAL CENTER
DEPARTMENT OF CONTINUING EDUCATION
and
BOSTON UNIVERSITY SCHOOL OF MEDICINE
DEPARTMENT OF OTOLARYNGOLOGY

announce three-day course

May 11-13, 1978

BOSTON UNIVERSITY MEDICAL CENTER

Course is designed for Laryngologists, Speech Pathologists and Voice Scientists and will address itself to voice physiology, voice pathology and organic disease of the larynx. Program will include papers, panel discussions and TV tape demonstrations of operating room procedures, including the use of the CO_2 laser.

Faculty will include both Laryngologists and Voice Scientists: Drs. David Brewer, Orin Brown, Raymond Colton, Lawrence DeSanto and W. James Gould.

Course is accredited by the AMA Physician's Recognition Award for 20 hours.

Registration limited to 80.

For further information write: M. Stuart Strong, MD, University Hospital, 75 East Newton Street, Boston, MA 02118.

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PRACTICAL CO_2 LASER SURGERY COURSE

at

BOSTON UNIVERSITY MEDICAL CENTER

MAY 18-19, 1978

Designed particularly for those individuals who have already had some experience with the CO_2 laser or expect to have one available in the near future. Course will include a brief review of the state of the art of the use of the CO_2 laser in the aero-digestive tract in a didactic setting. Thereafter the course will consist of an "on hands" demonstration in the dog laboratory where major resections of the oral cavity, pharynx, larynx and tracheobronchial tree using the laser will be demonstrated.

Faculty will include Dr. Albert Andrews of Chicago, in addition to members of the Department of Otolaryngology at Boston University School of Medicine.

For further information write: M. Stuart Strong, MD, University Hospital, 75 East Newton Street, Boston, MA 02118.

EAR RESEARCH INSTITUTE

Announces a Two-Week

TEMPORAL BONE SURGICAL DISSECTION COURSE

Course will demonstrate the multiple approaches to the structures of the temporal bone as currently used by members of the Otologic Medical Group, Inc.

Each day course members spend four hours in the dissection laboratory and four hours observing live color telecasts of surgery which correlates with the dissection of the day. Evenings are devoted to lectures illustrated by slides and motion picture demonstrations. Video tapes in color from the Institute's Otologic Seminar Library are available for study by course participants.

Twenty-four board certified or board eligible otolaryngologists and residents will be accepted in each course. Courses will be presented: March 6-17 and May 1-12, 1978. Tuition fee for otolaryngologists is $1200 and for residents $900 in United States currency. Applications of residents must be accompanied by a letter from their Chief of Service.

For further information: Fred H. Linthicum, MD, Director of Education, Ear Research Institute, 256 South Lake Street, Los Angeles, CA 90057.

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CURRENT CLINICAL CONCEPTS in OTOLARYNGOLOGY 1978

Konover Hotel, Miami Beach, Florida

MARCH 22-24, 1978

Current Clinical Concepts has been designed to provide a synopsis of recent advances and trends in the diagnosis and treatment of disorders and diseases of the head and neck.

March 22 — OTOLOGY, CANCER AND OTHER TUMORS, ENDOSCOPY.
March 23 — LARYNGOLOGY, RECONSTRUCTIVE PLASTIC, TRAUMA, GENERAL, AUDIOLOGY AND OTHER MODERN METHODS.
March 24 — NEUROTOLOGY, COSMETIC PLASTIC.

Program Chairman: JAMES R. CHANDLER, MD

Guest Speakers: Drs. R. J. Bellucci, R. J. Farrior, R. R. Gacek, A. M. Noyek, E. Skolnik, J. S. Turner, Jr., P. H. Ward.

Sponsor: Department of Otolaryngology, University of Miami School of Medicine, Miami, Florida.

Course Hours — 15 Category I

Information: Division of Continuing Medical Education, University of Miami School of Medicine, P. O. Box 520875, Miami, FL 33152. Tel. (305) 547-6716.

THE PAGE AND WILLIAM BLACK
POST-GRADUATE SCHOOL OF MEDICINE
OF THE MOUNT SINAI SCHOOL OF MEDICINE (CUNY)

Announces Postgraduate Courses

RHINOPLASTY AND OTOPLASTY

(Co-sponsored with The American Academy of Facial Plastic and Reconstructive Surgery, Inc.)

Under the Direction of
SIDNEY S. FEUERSTEIN, M.D.
Course Director
JACOB S. ARONOFF, M.D.
SAMUEL M. BLOOM, M.D.
WILLIAM LAWSON, M.D., D.D.S.
and Guest Faculty
JOHN CONLEY, M.D., New York, N. Y.
ROBERT SIMONS, M.D., Miami, Florida
RICHARD WEBSTER, M.D., Boston, Mass.
HOWARD SMITH, M.D., D.D.S.,
New Haven, Conn.
EUGENE TARDY, JR., M.D., Chicago, Ill.

June 11-15, 1978
Sunday through Thursday
9:00 A.M. to 6:00 P.M. (5 Sessions)

This course covers the basic principles of rhinoplasty including reconstructive surgery of the nasal septum and otoplasty. Basic lectures on surgery of the nasal tip will be thoroughly reviewed and discussed. Laboratory dissection on fresh cadavers will be coordinated with the lectures in addition to daily live and taped televised surgery. Anatomy, physiology, pathology, diagnosis, planning and evaluation in Rhinoplasty will be thoroughly reviewed. Management of the nasal septum with and without Rhinoplasty will be presented. Correction of nasal deformities including thorough discussion of component parts and their relation to every other part with special emphasis on the nasal tip and nostrils, splinting, correction of accompanying chin deformities, use of grafts for restoration of contour, plastic surgery in children and psychiatric aspects will be reviewed. Management of nasal deformities associated with cleft palate and cleft lip will be presented.

The technique and latest concepts developed in Rhinoplasty will be discussed and taught including the prevention and correction of Rhinoplasty sequelae. The importance of surgical judgment, proper association of the aesthetic and physiological requirements and methods of improvisation will be stressed.

Lectures on Otoplasty will deal with etiology, pathology and surgery of deformities of the auricle secondary to errors in shape, size and position.

FEE: $550

COSMETIC SURGERY OF THE AGING EYE

(Co-sponsored with The American Academy of Facial Plastic and Reconstructive Surgery, Inc.)

Under the Direction of
MORRIS FELDSTEIN, M.D., F.A.C.S.
and Faculty

June 16-17, 1978
Friday and Saturday
9:00 A.M. to 5:00 P.M. (2 Sessions)

The course is designed for those surgeons who have had some experience in this field and wish more exhaustive and detailed instruction in cosmetic surgery as it applies to the eye. In addition to lectures and films, a seminar format will be employed so that each participant will be able to resolve his particular difficulties in group discussions.

Cadavers for surgery will be provided. Admission only after correspondence with the Director of The Page and William Black Post-Graduate School of Medicine.

FEE: $250

FACIAL PLASTIC SURGERY

(Co-sponsored with The American Academy of Facial Plastic and Reconstructive Surgery, Inc.)

Under the Direction of
WILLIAM LAWSON, M.D., D.D.S.
Course Director
JACOB S. ARONOFF, M.D.
SIDNEY S. FEUERSTEIN, M.D.
and Guest Faculty

June 19-20, 1978
Monday and Tuesday
9:00 A.M. to 6:00 P.M. (2 Sessions)

This course will cover the face lift procedure. It will include lectures on case selection, operative technics, complications and results. Cadaver dissection and surgical demonstrations will be utilized.

Admission only after correspondence with the Director, The Page and William Black Post-Graduate School of Medicine.

FEE: $250

As an organization accredited for continuing medical education. The Page and William Black Post-Graduate School of Medicine of the Mount Sinai School of Medicine (CUNY) certifies that these continuing medical education offerings meet the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association, provided they are used and completed as designed.

APPLY TO: Director, The Page and William Black Post-Graduate School of Medicine, Mount Sinai School of Medicine, Fifth Avenue and 100th Street, New York, New York, 10029. Tel.: (212) 650-6737.

INFORMATION FOR AUTHORS

Send manuscripts by first-class mail to Editor Ben H. Senturia, MD, 4949 Forest Park Blvd., St. Louis, MO 63108, or to Coeditor Brian F. McCabe, MD, University of Iowa Hospitals, Iowa City, IA 52242. Original manuscripts dealing with clinical and scientific aspects of otolaryngology, bronchoesophagology, head and neck and maxillofacial and plastic surgery, audiology, speech pathology and related specialties will be considered for publication. It is understood that the manuscripts have not appeared in any other journal except society transactions.

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REFERENCES. All citations must be numbered in the order of appearance in the text. They should be listed chronologically on a separate sheet (double-spaced) at the end of the paper and should follow *AMA Style Book/Editorial Manual.*

Example (for journals): Stebbins WC, Miller JM, Johnsson LG, et al: Ototoxic hearing loss and cochlear pathology. Ann Otol Rhinol Laryngol 78:1007-1025, 1969

Example (for books): Berne E: *Group Treatment.* New York, Oxford University Press, 1966, p 26. Should there be any questions, please consult recent publications of the ANNALS.

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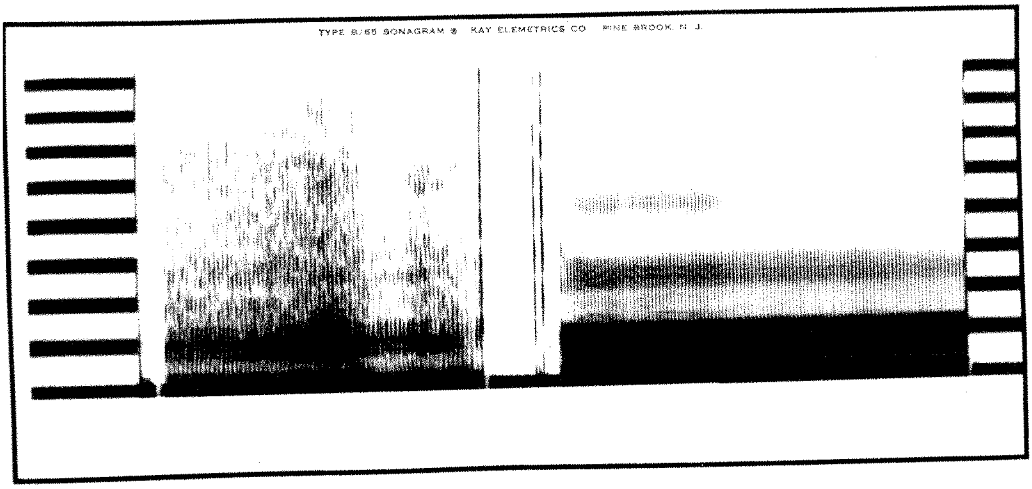

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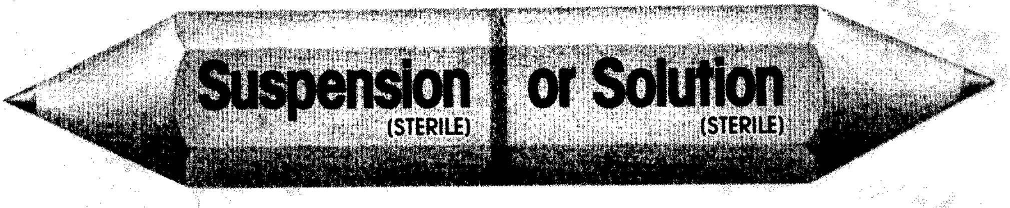

INDICATIONS:
For the treatment of superficial bacterial infections of the external auditory canal caused by organisms susceptible to the action of the antibiotics, and for the treatment of infections of mastoidectomy and fenestration cavities caused by organisms susceptible to the antibiotics.

DESCRIPTION:
Each cc contains: Aerosporin® brand
Polymyxin B Sulfate .... 10,000 units
Neomycin Sulfate .... 5 mg
(equivalent to 3.5 mg neomycin base)
Hydrocortisone .... 10 mg (1%)
The vehicle contains the inactive ingredients cetyl alcohol, **propylene glycol,** polysorbate 80, **purified water and** thimerosal (preservative) 0.01%.

PRECAUTIONS:
This drug should be used with care in cases of perforated eardrum and in long-standing cases of chronic otitis media because of the possibility of ototoxicity caused by neomycin.

ADVERSE REACTIONS:
Neomycin is a not uncommon cutaneous sensitizer. There are articles in the current literature that indicate an increase in the prevalence of persons sensitive to neomycin.

BENEFITS:
Indications include infections of mastoidectomy and fenestration cavities caused by organisms susceptible to the antibiotics.

INDICATIONS:
For the treatment of superficial bacterial infections of the external auditory canal caused by organisms susceptible to the action of the antibiotics.

DESCRIPTION:
Each cc contains: Aerosporin® brand
Polymyxin B Sulfate .... 10,000 units
Neomycin Sulfate .... 5 mg
(equivalent to 3.5 mg neomycin base)
Hydrocortisone .... 10 mg (1%)
The vehicle contains the inactive ingredients glycerin, hydrochloric acid, **propylene glycol, purified water and** potassium metabisulfite (preservative) 0.1%.

PRECAUTIONS:
This drug should be used with care when the integrity of the tympanic membrane is in question because of the possibility of ototoxicity caused by neomycin.

ADVERSE REACTIONS:
Neomycin is a not uncommon cutaneous sensitizer. There are articles in the current literature that indicate an increase in the prevalence of persons sensitive to neomycin. Stinging and burning have been reported when this drug has gained access to the middle ear.

BENEFITS:
Clear visualization of field. Does not have to be shaken.

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS COMMON TO BOTH PRODUCTS
CONTRAINDICATIONS:
In individuals who have shown hypersensitivity to any of the components, and in herpes simplex, vaccinia, and varicella.
WARNINGS:
Prolonged treatment may result in overgrowth of nonsusceptible organisms and fungi. If the infection is not improved after one week, cultures and susceptibility tests should be repeated to verify the identity of the organism, and to determine whether therapy should be changed.

When using neomycin-containing products to control secondary infection in the chronic dermatoses, such as otitis externa, it should be borne in mind that the skin in these conditions is more liable than is normal skin to become sensitized to many substances, including neomycin. The manifestation of sensitization to neomycin is usually a low grade reddening with swelling, dry scaling, and itching; it may be manifest simply as a failure to heal. During long-term use of neomycin-containing products, periodic examination for such signs is advisable and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for that patient thereafter.
PRECAUTIONS:
If sensitization or irritation occurs, medication should be discontinued promptly. Patients who prefer to warm the medication before using should be cautioned against heating the solution above body temperature, in order to avoid loss of potency.

Treatment should not be continued for longer than ten days. Allergic cross-reactions may occur which could prevent the use of any or all of the following antibiotics for the treatment of future infections: kanamycin, paromomycin, streptomycin, and possibly gentamicin.
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- Wide range of antibacterial activity, including action against many strains of *Pseudomonas aeruginosa* and *Proteus*
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HEARING LOSS after EUSTACHIAN TUBE LIGATION MEASURED ELECTROCOCHLEOGRAPHICALLY

NONINVASIVE CHRONIC RECORDING OF AUDITORY NERVE POTENTIALS

Michael L. Wiederhold, PhD
Serge A. Martinez, MD
Dana M. Paull, AB
Martha G. Pierson, PhD
Hugh O. deFries, MD

EFFECTS OF EUSTACHIAN TUBE LIGATION ON AUDITORY NERVE RESPONSES TO CLICKS

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Robert E. C. Scott, BS
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NONINVASIVE CHRONIC RECORDING OF AUDITORY NERVE POTENTIALS

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Martha G. Pierson, PhD
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Bethesda, Maryland

SUMMARY — A system is described which allows repeated, noninvasive recording of auditory nerve responses in the cat to transient acoustic stimuli using a closed acoustic system. N_1 responses to clicks are recorded from a stainless steel ring electrode at the end of a hollow earbar, the tapered end of which is made of insulating plastic. Acoustic stimuli are generated by a dynamic earphone coupled to the earbar. A calibrated probe microphone is also incorporated into the earbar to measure sound pressure near the tympanic membrane. This allows better stimulus control than is available with free-field systems. To facilitate insertion of the earbar, meatoplasties were performed on all animals. Responses recorded with this system in anesthetized cats are described and compared with those recorded at the round window. Good repeatability of measurements is described for an animal population of 20 domestic cats over a period of several months. For some of these animals, response amplitude varied from one session to another, but response latency, especially for condensation clicks, was consistent. By comparing statistics of multiple measurement of both N_1 amplitude and latency for rarefaction and condensation clicks, it is concluded that the N_1 latency vs click-level function for condensation clicks provides the most reliable measure of the cat's auditory nerve function.

In order to study the long-term effects of various agents or procedures on the hearing of experimental animals, an objective measure of responses to both threshold and suprathreshold acoustic stimuli is needed. Although behavioral methods have been used to great advantage in measuring changes in the acoustic threshold at which an animal will respond,[1] the techniques of electrocochleography (ECochG)[2] offer the additional advantages of objectivity, a measure of suprathreshold responses and independent assessment of the peripheral auditory system.

In order to use ECochG to study slowly developing and possibly small hearing losses, two conditions must be met: 1) accurate stimulus control and 2) a noninvasive recording technique. Closed acoustic systems, incorporating a calibrated probe microphone to measure sound pressure near the tympanic membrane (TM), have provided excellent stimulus control for experimentation in auditory physiology.[3] Coats and Dickey[4] and Montandon et al[5] have documented that auditory nerve responses to clicks, very similar to those recorded near the round window of the cochlea, can be recorded from the external ear canal of cats. This paper describes a means of recording auditory nerve responses combining these two techniques.

Our primary objective was to study the development of hearing loss following induction of middle ear effusions by Eustachian tube ligation as reported in the following paper.[6] However, the system developed for chronic recording is applicable to many types of insults to the auditory system, such as sound exposure, ototoxic drugs or other environmental factors, and is described separately here. To elaborate upon our experience using this system over a period of one year on a population of 20 healthy, young cats, we assess the repeatability of measurements and the evaluation of parameters which might best describe a decrement in auditory nerve function.

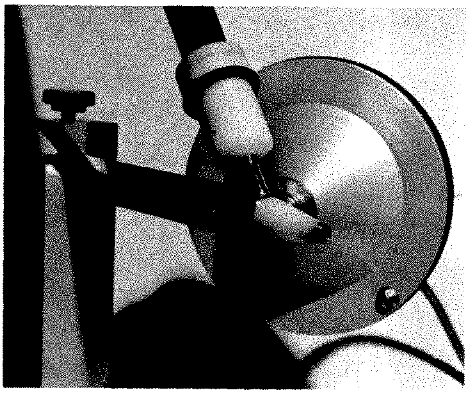

Fig. 1. Closed acoustic and recording system. The earbar fits into a standard stereotaxic instrument. The large conical structure encloses a dynamic earphone. A small stainless steel ring at the narrow end of the earbar serves as the recording electrode. The open volume of the tapered portion of the earbar (behind the recording ring) and the coupler to the earphone are filled with steel wool to provide acoustic damping.

METHODS AND MATERIALS

Both acoustic stimulation and response recording were performed with the closed system illustrated in Figure 1. The larger conical structure in the rear couples the enclosed earphone used for sound stimulation (Koss pro 4AA*) into the hollow earbar (horizontal, foreground). The tapered portion of the earbar is made of an insulating plastic except for the stainless steel ring (3.5 mm outside diameter at tip) which serves as the recording electrode. A small lead, soldered to the inside of the ring, extends through the tapered portion to connect to the amplifier head stage. Projecting from the top of the earbar is a probe tube leading to a monitoring microphone, a General Radio** 1962-9602 1.27 cm electret microphone. The probe tube is of 1 mm inside diameter polyethylene and extends to within 3 mm of the earbar tip. A plug in the earbar provides a seal behind the entrance of the probe tube and earphone coupler. During a recording session the earbar is held in the external ear canal by a stereotaxic apparatus, and firmly maintained against the tympanic ring to assure good electrical contact. Additional support is provided by a bitebar head holder.

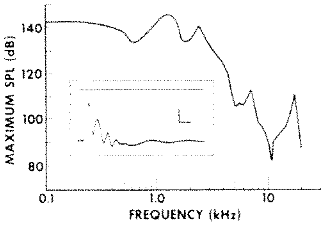

Fig. 2. Acoustic calibration of system. Main portion of figure gives sound pressure level in dB re 0.0002 dyn/cm^2 (SPL) near the TM in an animal with 1 V RMS presented to the power amplifier (0 dB attenuation). Inset shows 0 dB RC acoustic waveform measured with microphone in position of TM in 1 cc coupler. Upper trace is voltage pulse to power amplifier. Calibrations: 1 V for pulse to power amplifier, 104 dB SPL for acoustic transient and 0.5 msec for both. Peak pressure of click is 129 dB SPL.

For click stimuli, a 100 μsec square pulse is delivered to the earphone through a step attenuator (Hewlett-Packard† 350 D) and a power amplifier (Dynaco†† 120). For calibration of the frequency response of the system, a sinusoid swept between 100 Hz and 20 kHz was generated by a sweep oscillator (General Radio 1523 P2) and the output of the calibrated microphone was recorded on a level recorder (General Radio 1523). The method described by Pfeiffer[7] was used for calibration: the earbar tip is placed into a 1 cc plastic coupler and the sound pressure generated by the constant-voltage sinusoid is measured with the microphone both at a position corresponding to that of the TM and through the probe tube. This provides a calibration of the acoustic loss caused by the probe tube at each frequency. The sound pressure is then measured through the probe tube at all frequencies with the earbar in the ear canal. With the probe tube correction applied to these data, the sound pressure near the TM in the animal can be determined for constant voltage to the earphone at all frequencies. Such output for maximum input (0 dB attenuation), 1 V RMS to the power amplifier, is illustrated in Figure 2. It is evident that the system is far from ideal, having a considerable loss above 4 kHz. The click waveform recorded with the microphone at the position of the TM in the 1 cc coupler is illustrated in the inset of Figure 2. The peak pressure of the click (0 dB attenuation, 1 V pulse to power amplifier) is 129 dB re 0.0002 dyn/cm^2 (SPL). The upper trace of the inset illustrates the voltage pulse to the earphone. The acoustic travel time from the earphone to the tip of the earbar (68 mm) accounts for most of the 0.25 msec delay from the start of the pulse to the start of the acoustic transient.

The chronic cats used in this study are all from a population of 20 cats which were reared in an aseptic environment and obtained

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*Acoustech, Milwaukee, WI.

**Genrad Co., Bolton, MA.

†Hewlett-Packard, Palo Alto, CA.

††Dynaco, Inc., Blackwood, NJ.

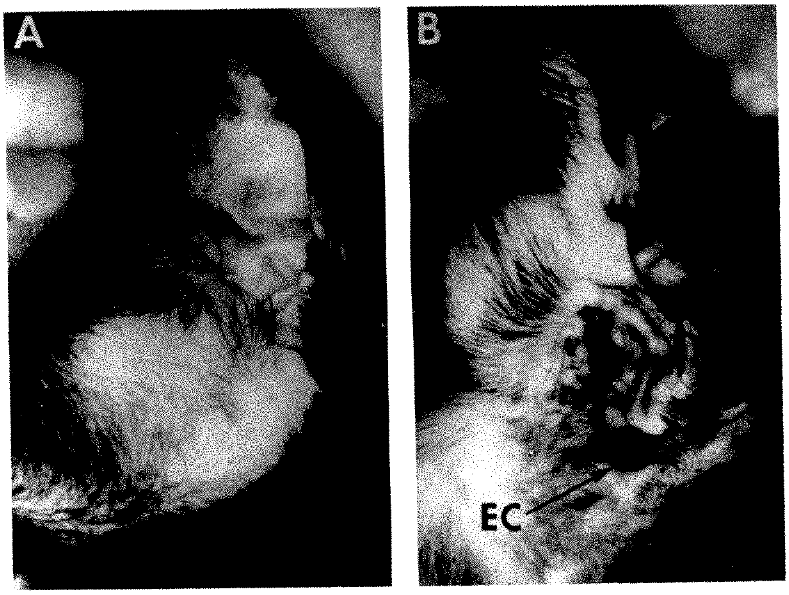

Fig. 3. External ear of normal cat (A) and one on which meatoplasty has been performed (B). Note that in normal cat the ear canal and TM are not visible, whereas in modified cat the entire ear canal (EC) and TM can be seen.

from Faunalabs* at the age of two months. These cats are now 16 months old. All have maintained excellent general health although, as reported below, two of them appear to have profound bilateral hearing losses. Because of the anatomical structure of the normal cat auricle, it was necessary to surgically revise the external auditory canals of our cat population to allow insertion of the earbar. The tragus, antitragus, and antihelix normally surround the entrance of the external canal, making insertion of a straight instrument extremely difficult. We have modified the external auditory canal by deflecting a section of the posterolateral auricular cartilage inferiorly, so that it lies ventral to the new orifice. Further modification of the lumen, with insertion of triangular skin flaps into the split canal cartilage, widens the canal and helps prevent postsurgical stricture. Figure 3 illustrates the normal external canal (A) and one modified according to the procedure described above (B). Postoperative care consisted of daily inspection of the surgical ears with frequent removal of crusts and cerumen. No potentially ototoxic antibiotics were administered. Sutures were removed at one week. After three weeks all ears were completely healed and ready for testing.

Responses were recorded from either the earbar electrode or, during acute experiments, from a wire electrode on the cochlea near the round window. These responses were amplified with a Grass P511 amplifier** used with a gain of 10,000x and a passband from 10 Hz to 10 kHz. This amplifier has an input resistance of 2 x 10^{11} ohms, so much greater than any expected contact resistance of the recording electrode, that variations in this contact resistance should have negligible effect on the amplitude of recorded responses. To improve the signal-to-noise ratio of recordings and to assure a free acoustic path to the TM, the external ear canal was carefully cleaned with a silver wax loop and cup forceps under an operating microscope before each recording session. During a recording session the animal, amplifier, and a battery-operated heating pad were within a sound-attenuated room. All other electronic equipment including the amplifier power supply were outside of this room. The cats were anesthetized with intramuscular ketamine, using an initial dose of 30 mg/kg and supplemental doses of 15 mg/kg every 45 minutes, or as needed. A single dose of 0.08 mg atropine to minimize secretions and 0.3 mg/kg acepromazine as a relaxant was given with the initial anesthetic. The same anesthetic was used for all acute experiments and for the surgical modification of the external auditory canals. During the recording session, temperature was monitored with a rectal thermistor probe and a heating pad was used to maintain body temperature between 36 and 39 C.

The amplified responses were averaged with an Ortec† 1621 averager, using a bin width (sampling interval) of 0.02 msec. The averager has 256 bins, so that a total period of 5.12

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*Faunalabs, Inc., Hudson, MA.

**Grass Instrument Co., Quincy, MA.

†Ortec, Inc., Oak Ridge, TN.

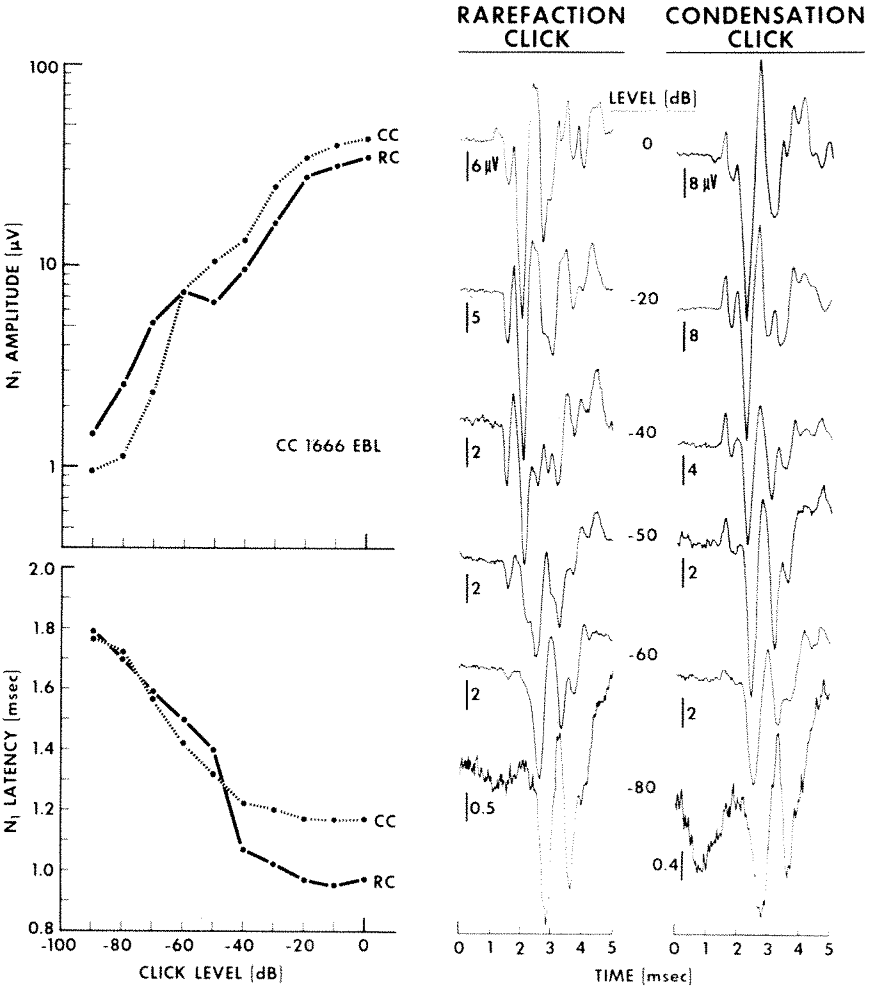

Fig. 4. Responses to rarefaction (RC) and condensation (CC) clicks recorded with the earbar electrode using the closed acoustic system. Click level given in dB attenuation from maximum level of 130 dB SPL peak pressure. Left) Amplitudes (upper plots) and latencies (lower plots) of averaged responses to clicks from 0 dB to −90 dB levels. Right) Samples of averaged responses from which the amplitudes and latencies were measured for both RCs and CCs. Calibration bar, in μV, is indicated to left of each average. Each average is of 256 responses for levels above −40 dB and 512 responses for −40 dB and below.

msec was averaged. At its maximum sensitivity, the resolution of the averager corresponded to a 0.1 μV signal. For larger responses, the sensitivity was reduced stepwise to 1μV. Although the maximum number of responses which this instrument will average is 128, the computer system employed can combine several of these averages to increase signal-to-noise ratio.

For this study clicks were presented at 10/sec. A trigger pulse started the averager 1.2 msec before the click pulse was delivered to the earphone. Each average was fed digitally to a PDP 11/45* computer. The computer averaged the 50 points in the first msec of each average (before the click was presented) to determine a baseline, and the voltage from this baseline to the maximum negative peak was measured to determine N_1 amplitude. Response latency was measured from the beginning of the click pulse to the earphone to the peak of the N_1 response. To convert the latencies presented in this paper to latency from the beginning of the acoustic transient at the

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*Digital Equipment Corp., Maynard, MA.

TM, 0.25 msec should be subtracted (see above).

RESULTS

Typical averaged responses to rarefaction (RC) and condensation (CC) clicks obtained from one of the chronic cats are illustrated in Figure 4. Responses to clicks at levels from 0 to −80 dB (re 130 dB SPL peak pressure) are shown in the right side of the figure. The amplitudes and latencies of the responses for the complete series are plotted on the left. The monotonic rise of N_1 amplitude with click level for CCs and the dip in the RC amplitude function at −50 dB are typical of what has been reported for round window recordings.[8] Also similar to the round window recordings are the smooth decline in N_1 latency with increasing level for CCs and the abrupt change at −40 dB for RCs. The cause of the changes at −50 and −40 dB in the RC functions can be seen in the averaged responses on the right for RCs at −60, −50, and −40 dB. As the click level is increased from −60 to −50 dB, a small, earlier peak is seen which makes the whole N_1 broader than at either −60 or −40 dB. With a further increase to −40 dB, the earlier peak dominates the response, and thus the latency shifts to a lower value. We have defined N_1 as the larger of the two peaks when there is such a splitting. Since, with increase of click level, the earlier peak grows gradually over 10-20 dB, the point at which the latency suddenly shifts to a shorter value will be that level at which the earlier peak first becomes largest. This shift will be discrete no matter how closely the click levels tested are spaced. Such splitting of N_1 seldom occurs with CCs. Thus, the CC latency function generally shows a more gradual change with click level.

To compare recordings from the earbar electrode with the more familiar round window recordings, several acute cats were prepared for both types of recordings, as is illustrated in Figures 5 and 6. Sample responses for the two recording methods are shown in Figure 5. Although the response amplitude is much lower using the earbar electrode, the shapes of the responses are quite similar at the lower click levels (−60 and −50 dB). At the higher levels (−40 and especially 0 dB) there are striking differences in the shapes of the responses. This is probably due to the larger contribution of the cochlear microphonic (CM) to the round window response. The first deflection of CM is indicated for the 0 dB response recorded from the round window (the earlier diphasic deflection is the artifact of the pulse to the earphone). Only a small CM component is seen in the earbar recording for the 0 dB click and its polarity is opposite to that recorded near the round window. It is evident that CM was reduced more than was

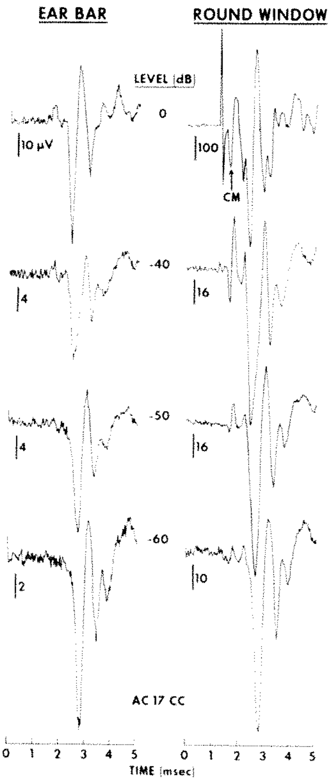

Fig. 5. Comparison of averaged responses from earbar electrode (left column) and a wire electrode 1 mm posteroventral to round window in the same acute cat (right column). Responses shown for 0, −40, −50, and −60 dB re 128 dB SPL peak pressure CCs. All averages are of 256 responses; calibration bars are as in Fig. 4.

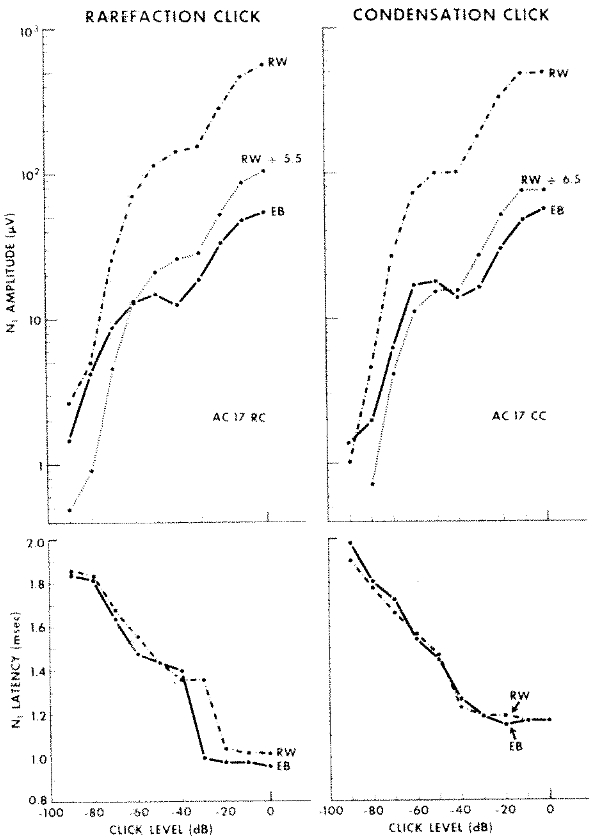

Fig. 6. N_1 amplitude and latency functions for RCs and CCs recorded both at the round window (RW) and earbar (EB). Same cat as in Fig. 5. All responses are averages of 256 responses for amplitudes above 10 µV and 512 responses for amplitudes less than 10 µV. Dotted lines represent round window amplitude divided by the average ratio of RW to EB amplitude for all click levels.

N_1 in the earbar recording, relative to recordings from the round window. Montandon et al[5] have drawn the same conclusion from their recordings in the cat. The relative attenuation of these two responses as they reach the earbar electrode may vary from one preparation to another. For example, there are larger CM responses, relative to N_1, in Figure 4 than in the earbar recordings of Figure 5.

N_1 amplitude and latency as a function of click level in response to both RCs and CCs for the two electrodes are illustrated in Figure 6. If the responses recorded with the earbar electrode were a constant fraction of the round window responses, the two level functions would be displaced vertically by a constant distance on these logarithmic plots. The average logarithmic displacement was computed and the dotted line in the amplitude functions represents the round window amplitude reduced by this factor. It is clear that the two functions are not so simply related. This may be due to the addition of CM to neural responses at high click levels. As noted above, CM is larger, relative to N_1, in round window recordings than in earbar recordings and the CM polarity is reversed between the two. Thus, at a given point in the N_1 response, CM could add to N_1, with a large contribution, in the round window recording and subtract from N_1, with a smaller contribution, in the earbar recording. Since CM reverses polarity between

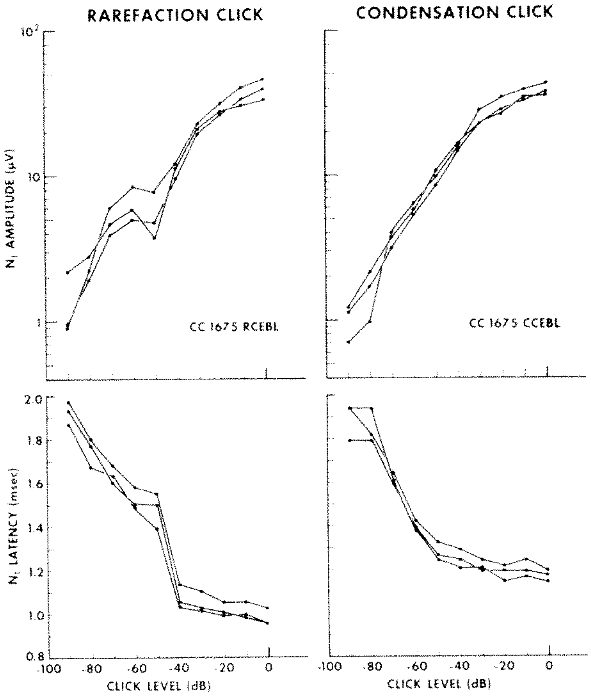

Fig. 7. N_1 amplitude and latency functions for RCs and CCs on three repeated recording sessions for one chronic cat. For 0 dB RC responses, that of intermediate amplitude was recorded 3 weeks after meatoplasty, that of lower amplitude 1 week later, and that of highest amplitude 11 weeks after the second session.

RCs and CCs, it might be expected that CM would increase the measured N_1 for one polarity of click and decrease N_1 for the other polarity. Actually the contribution of CM to the N_1 recordings could be nearly equal for both polarities since, at high levels, the difference in N_1 latencies between RCs and CCs (0.2 msec) is nearly the same as the time difference between one positive peak of CM and its next negative peak.

The contamination of N_1 by CM with our round window recordings is caused by the extensive ringing of the present click stimulus (Fig. 2). With a briefer click, as can be obtained with a condenser earphone,[3] the CM response is generally completed before N_1 begins and thus does not interfere with measurements of N_1. Since the CM contribution is relatively small in the earbar recordings, the ringing of our click does not seriously degrade these recordings. The reduction in CM in the earbar recordings resembles that seen with recordings from a concentric electrode in the internal auditory meatus.[8,9]

Despite the differences in response shape and N_1 amplitude functions for the two electrodes, the latency functions correspond well to one another, especially for CCs, as shown in the lower portion of Figure 6. The difference in the levels at which the latency changes suddenly for RCs is probably not significant since we only made measurements in increments of 10 dB. Since the level at which the sudden change occurs is actually discrete, (see above), a small change in sensitivity could cause the apparent 10 dB shift. The two functions in Figure 6 were measured sequentially, separated by one hour, and thus a small change in sensitivity could have occurred.

It is important to determine whether recordings are stable from one test session to another. Figure 7 illustrates amplitude and latency functions for one ear from three recording sessions. The first recording session (intermediate N_1 amplitude for 0 dB RCs) occurred 3 weeks following meatoplasty, the second session (lowest N_1 amplitude for 0 dB RCs) 1 week later, and the third session 11 weeks after the second. Except for differences in the region of the sudden latency shift for RCs, all four functions were similar for all three recording sessions, indicating test-retest reliability.

On a number of occasions the N_1 amplitudes for the same level clicks were considerably different, but the latencies were nearly the same. In extreme cases the N_1 amplitude during one session was lower than in another by as much as a factor of seven without there being a significant change in the latency functions. The amplitude of a given response depends upon the degree of electrical coupling between the electrode and the site of generation of the response being recorded, which for N_1 is presumably the auditory nerve within the cochlea and internal auditory canal. Since the input resistance of the amplifier we used is very large compared to any expected electrode contact resistance (see Methods and Materials), the latter is not likely to affect the response amplitude. However, the currents flowing from the cochlea to the external ear canal, which generate the potentials recorded there, are likely to vary greatly along the length of the canal. Thus the point along the canal at which the ring electrode makes contact will significantly affect the response amplitude. Recordings with lowered amplitudes but normal latencies probably result when the recording tip of the earbar was not inserted all the way to the tympanic ring. We interpret such findings to mean that the response at the cochlea had not changed, but that our ability to record it at the ear canal had decreased. Since response latency did not change significantly in these circumstances, latency represents a more consistent parameter of the response than does amplitude.

On some occasions the N_1 amplitude was reduced and its latency increased, compared to previous recordings. This would be expected if the sound reaching the TM were attenuated. Such attenuation can occur if the lumen of the earbar is obstructed in any way, either by cerumen, fluid, or the canal wall itself. Thus it is imperative that the earbar tip be concentric with the TM and that the ear canal and TM be free of cerumen and any fluid. After rechecking for obstruction or misalignment, most cases of apparent sound attenuation were rectified.

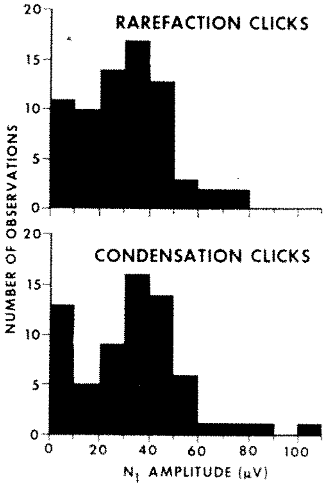

Fig. 8. Distribution of N_1 amplitudes recorded with the earbar electrode for 0 dB clicks in 72 separate recordings. For most animals both ears were recorded on the same day, but the two ears are considered separate recordings for these distributions. For RCs, the average amplitude is 30 μV (72 recordings), while for CCs the average amplitude is 32 μV (68 recordings).

The distributions of N_1 amplitudes for RCs and CCs at 0 dB from 72 recording sessions are presented in Figure 8. There is a large range of amplitudes with the overall average being 31 μV. The concentration of low amplitudes (i.e., those below 20 μV) could result either from poor earbar placement or obstruction of the earbar tip, as discussed above, or from a hearing defect in the cat. It is felt that 2 of the 20 cats suffered profound bilateral hearing losses since we were unable to record responses to clicks below 0 or −10 dB on at least four separate testings. In both of these cats, patent ear canals allowed excellent visualization of their

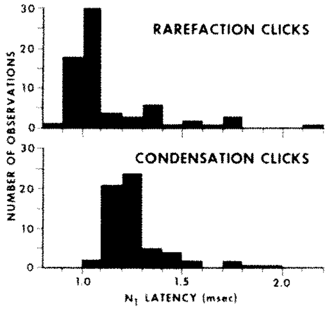

Fig. 9. Distribution of N_1 latencies for 0 dB RCs and CCs recorded with the earbar electrode. Same responses as indicated in Fig. 8.

TMs, thus ruling out obstruction of the sound source as a cause of absent responses. In one of these cats, round window recording was attempted after the fourth earbar recording session, and even at the round window no responses were obtained below 0 dB. Even disregarding the lower amplitude responses, there is a large variation, from 20 to over 100 μV at 0 dB. Thus amplitude does not appear to be a consistent measure of response across the population of animals.

In contrast to the broad distribution of N_1 amplitudes observed, the latencies for 0 dB clicks were rather tightly grouped, as illustrated in Figure 9. For RCs, 69% of the responses had latencies between 0.9 and 1.1 msec and for CCs, 73% lie between 1.1 and 1.3 msec. Again long latencies could be due to either an obstruction of the sound source or a hearing loss in the cat. Six of the recordings with latency greater than 1.1 msec for RCs and four of those greater than 1.3 msec for CCs were from one of the animals concluded above to have a profound hearing loss.

Responses to 0 dB clicks with low amplitude and long latency are what might be expected from an abnormal ear. The individual latency-vs-click level plots for recordings with 0 dB RC latency below 1.1 msec or 0 dB CC latency below 1.3 msec all appeared similar (except for the point at which the sudden change occurs for RCs), even for those with low amplitudes. Thus we are inclined to place much more confidence in measurements of latency than of amplitude. Similar conclusions have been drawn by several other investigators.[5,10-12] In fact, if there is fluid in the middle ear, N_1 amplitude can actually increase when the latency function indicates a hearing loss, as demonstrated in the following paper.[6] The discontinuity in the RC latency functions and the variability among recording sessions of where this occurs when testing in 10-dB steps makes the CC latency functions more useful for comparisons across animals or from one test session to another in the same animal.

On six occasions, 0 dB N_1 amplitudes greater than 20 μV, but latencies greater than 1.3 msec for CCs or 1.1 msec for RCs were obtained. When the complete amplitude and latency function for these cases are compared to the "normals" they are seen to be shifted significantly to the right even though the N_1 amplitudes in these cases were large. From such observations we now consider the values of 1.1 msec for RCs and 1.3 msec for CCs to be the maximum latencies which represent normal responses to 0 dB clicks in our population of cats. We interpret all cases (in which obstruction of the sound source was ruled out) with 0 dB N_1 latencies greater than these values to indicate a hearing loss.

DISCUSSION

The data presented here indicate that our new system provides reliable evaluation of an experimental animal's auditory nerve function. Its major advantage over similar methods reported are the accurate stimulus control and the noninvasive method of recording responses. It is of interest that the responses we record from the cat ear canal are much larger than those usually recorded from humans.[4,5,10,13] This probably reflects both a better electrical coupling from the cochlea to the ear canal in the cat and a greater N_1 response generated in the cochlea of the cat, since transtympanic recordings from the human seldom exceed 30 μV in amplitude,[12-15] whereas in the cat, round window N_1s can exceed 500 μV.[8,9]

Although the differences between CCs and RCs in N_1 amplitude and latency functions have been made explicit for round window and auditory nerve recordings some time ago,[8] they have been largely ignored in descriptions of ECochG, although Davis[2] clearly states the complications that can occur if these differences are ignored. If one were to combine responses to RCs and CCs[14] or use random-phase noise pips or tone pips, it is evident that at higher levels (−40 to 0 dB in Fig. 4), peaks would be added that were shifted in time by a considerable fraction of their duration. This will broaden the peaks and lower their amplitude, compared to the responses to stimuli of a fixed phase. Also, in such combined responses, a shift in latency at a level corresponding to −50 to −40 dB in Figure 4 and possibly a dip in the amplitude function would occur. Since the amplitude and latency functions both increase smoothly with level for CCs, it may be misleading to ascribe responses to high- and low-level stimuli to qualitatively different mechanisms, as has been done often.[14,16,17] Rather, it appears that the irregularities in the RC functions are due to changes in the preferred times at which auditory nerve fibers generate action potentials. For example, the broad, split peak and lower N_1 amplitude for −50 dB RCs in Figure 4 could be due to fibers firing at two slightly different preferred times. Above and below this level, the fibers contributing to N_1 presumably fire at the earlier (−40 dB) or the later (−60 dB) time, and the greater synchrony at these levels produces larger responses than at −50 dB. At sound pressure levels below that at which N_1 splits, the latency increases more rapidly, probably due to the predominant contribution of auditory nerve fibers with lower characteristic frequencies, as discussed by several investigators.[2,13,18,19] Since our click stimulus does have relatively higher energy at low frequencies (Fig. 2), this will have a significant effect at the lower click levels. In the modeling of Elberling,[18] the clear emergence of two portions in both the amplitude and latency functions are taken as further evidence of two mechanisms. However, since the model is based on responses to low-frequency rarefaction clicks only, the two portions of the response functions are insured.

Our criteria of "normal" hearing will be used for establishing which animals will be used in a long-term study.[6] Rather than comparing results at a given point in a study with the average normal response functions, it would be preferable to observe changes within a given animal. For this reason we have used repeated recordings to establish a reliable "baseline" on each animal in our colony. This will allow a more accurate determination of the hearing loss caused by experimental procedures than is usually the case in clinical studies, where the function of a system or organ before receiving an insult is seldom well-documented.

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EFFECTS OF EUSTACHIAN TUBE LIGATION ON AUDITORY NERVE RESPONSES TO CLICKS

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SUMMARY — Auditory nerve responses to condensation and rarefaction clicks were recorded from the external ear canal of cats using a closed acoustic system. Repeated control recordings from both ears formed a baseline for each of four animals used in this study. After a baseline had been established, the Eustachian tube on one side was ligated and serial recordings of N_1 responses were performed for up to 140 days postligation. By comparing the shift which occurred in the N_1 latency-vs-click level plots after ligation, the equivalent hearing loss was determined. In all cases where the Eustachian tube was successfully ligated, the loss was progressive for the first 20 days, then usually showed some transitory improvement. The loss stabilized after 60 days, varying from 15 to 40 dB in different animals. In addition to N_1 recordings, serial tympanograms were also measured. These indicated negative middle ear pressure in the first two days postligation and the presence of middle ear fluid by one week postligation.

Middle ear effusions in the experimental animal have been produced by several researchers over the past 60 years. The use of wooden pegs inserted into the Eustachian tube (ET) openings,[1] ligation of the tubal opening in the nasopharynx,[2] electrocautery of the ET lumen,[3] ligation of the ET at the basisphenoid[4] and, recently, introduction of bacteria into the middle ear[5] have all resulted in the production of effusions in the mastoid bulla. Bacteriologic, biochemical, and cytologic studies of the effusions have produced considerable knowledge concerning the pathogenesis of these effusions. However, to date, no report has appeared in the literature concerning the effects of chronically induced middle ear effusions on the function of the cochlea of the experimental animal. It was the aim of this study to measure hearing loss induced by sterile ligation of the ET in the cat and to follow its time-course over several months. All cats used in this study, whether labeled AC or CC, were maintained on a chronic basis.

To quantify changes in cochlear function following ET ligation, we used auditory nerve responses to clicks recorded with a closed acoustic system, as described in the preceding paper.[6] N_1 responses to click stimuli were recorded from the external auditory canal, close to the tympanic membrane (TM). Both amplitude and latency of N_1 in response to rarefaction (RC) and condensation (CC) clicks were measured over a wide range of click sound pressure levels. A baseline was established from such measurements for each animal prior to tubal ligation. Changes from the baseline were used to evaluate the hearing losses experimentally induced in the present study.

The four cats used in this study underwent ligation of one ET, with the opposite side left intact as a normal control. As a result of ET ligation, middle ear effusions were induced in each animal as determined by observation, tympanometry, and subsequent myringotomy. These effusions caused a shift in the N_1 latency-vs-sound pressure level functions corresponding to a hearing loss of from 1.5 to 40 dB. This study also demonstrates that the system described earlier[6] does provide sufficiently stable recordings to assess the effects of middle ear effusions on the auditory nerve responses to clicks, and to determine the time-course of the induced hearing loss.

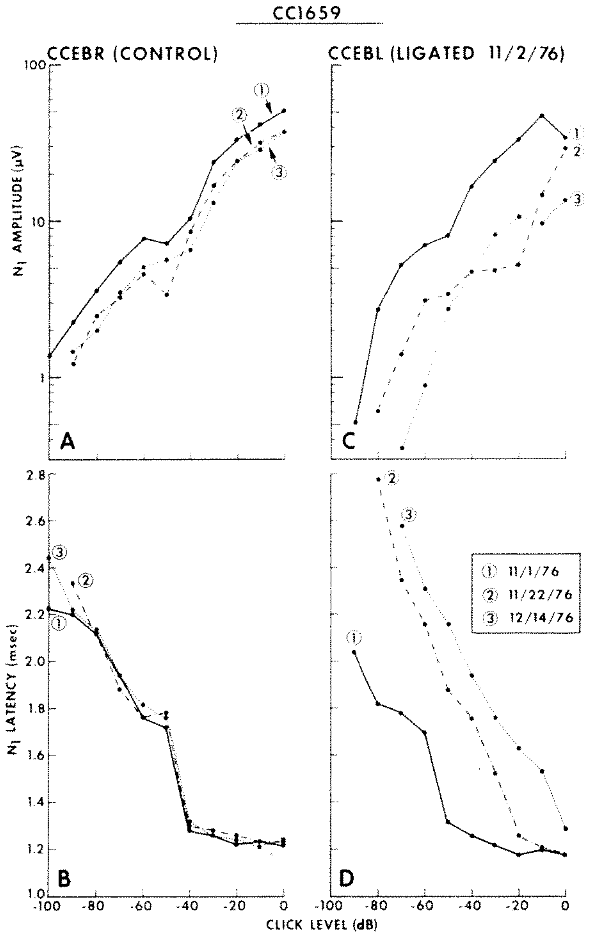

Fig. 1. Plots of N_1 baseline-to-peak amplitude (A and C) and latency-vs-sound pressure level (B and D) for condensation clicks from three recording sessions on CC 1659. The Eustachian tube of the left ear (C and D) was ligated on 11/2/76; right ear (A and B) is normal control. Level series 1 was obtained 1 day before ligation, series 2 at 20 days postligation, and series 3 at 42 days postligation. Average shift for latencies between 1.3 and 2.0 msec for series 2 in part D is 33 dB; for series 3, it is 40 dB, relative to series 1. EB - Recordings made with earbar electrode.

METHODS AND MATERIALS

Baseline electrocochleographic (ECochG) recordings were obtained during a minimum of three recording sessions for three of the four cats used in this study. These were recorded over a period of several months prior to ET ligation and included preoperative recording on the day of ligation. Only one recording session was performed prior to ligation of the ET of the fourth cat (AC 18). Concomitant with these recordings, tympanometric evaluation of TM compliance was also performed using the American Electromedics tympanometer with a 220 Hz probe tone.

The animals were anesthetized for recording sessions and for all surgical procedures with intramuscular ketamine, 30 mg/kg, with supplemental doses of 15 mg/kg every 45 minutes or as needed. All cats in this study received bilateral meatoplasties to facilitate insertion of the recording earbar (see below). The ETs were approached through a submandibular approach similar to that described by Proud and Odoi,[4] but from a more submental direction. Extending laterally and deep toward the bulla, a groove was identified and followed directly to where the ET enters the bulla. After the ET was separated from its enclosing muscle fibers, it was doubly ligated with a 4-0 silk ligature. The incision was then closed with 3-0 chromic subcutaneous sutures and 4-0 nylon skin sutures. No antibiotics were administered postoperatively.

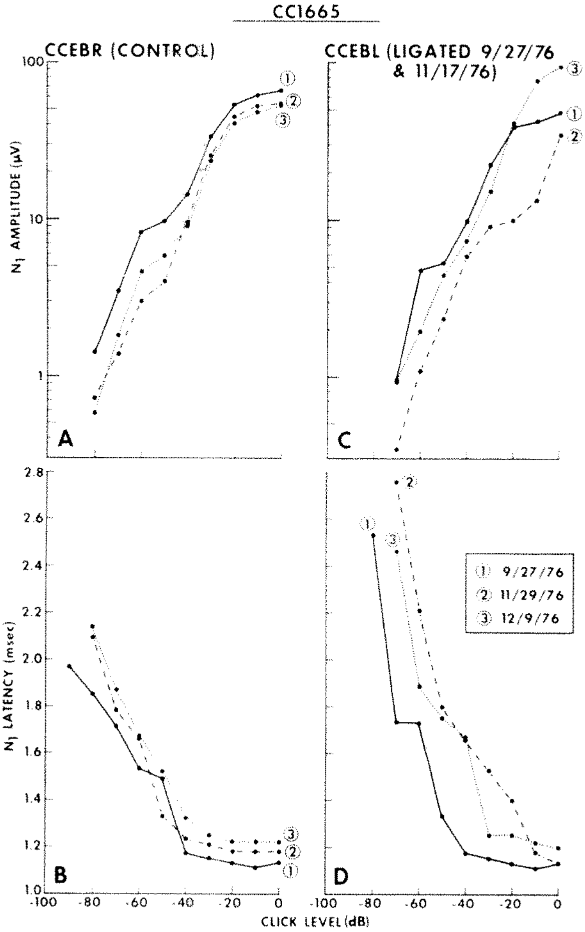

Fig. 2. N_1 amplitude and latency functions similar to Fig. 1 for three recording sessions from CC 1665. In this cat the left ET was ligated twice on 9/27/76, after which the ET recanalized and again on 11/17/76 (see text). Baseline series 1 was obtained preoperatively on 9/27/76. Series 2 was obtained 12 days after the second ligation, and the average shift in the CC latency function (D) was 24 dB. Series 3 was obtained 22 days after second ligation; average shift was 16 dB.

Auditory nerve responses to condensation (CC) and rarefaction (RC) clicks were recorded from the external auditory canals using the system described in the preceding paper.[6] Briefly, a dynamic earphone is coupled to a hollow earbar assembly which seals into the ear canal to provide acoustic stimuli. A probe tube extends to within 3 mm of the TM, allowing accurate monitoring of the stimulus during a recording session. The most intense click stimuli used in this study had a peak pressure of 130 dB SPL, and SPLs are presented in dB attenuation from this level. The tapered end of the earbar is made of a nonconducting plastic except for a small stainless steel ring at its tip which serves as the recording electrode. The amplitude and latency of the N_1 responses were measured from the average of 200 to 1000 responses to identical stimuli in each condition.

Recordings were conducted on the first postoperative day and then on a weekly basis, with an evaluation period of 140 days for the first cat and 70 days for the fourth. One cat (CC 1665) was noted to have near-normal responses in the ligated ear on the 50th postoperative day. Tympanometric patterns were also normal at this time. Surgical reexploration disclosed loosening of the silk ligature and recanalization of the ET. The ET was then religated and divided, and the divided ends of the tube were buried into the adjacent pharyngeal musculature. This procedure was also followed on the initial ligation for CC 1675 and CC 1659. After adopting this procedure, the time-course of hearing loss was similar for all animals including AC 18, which had received only a simple ligation.

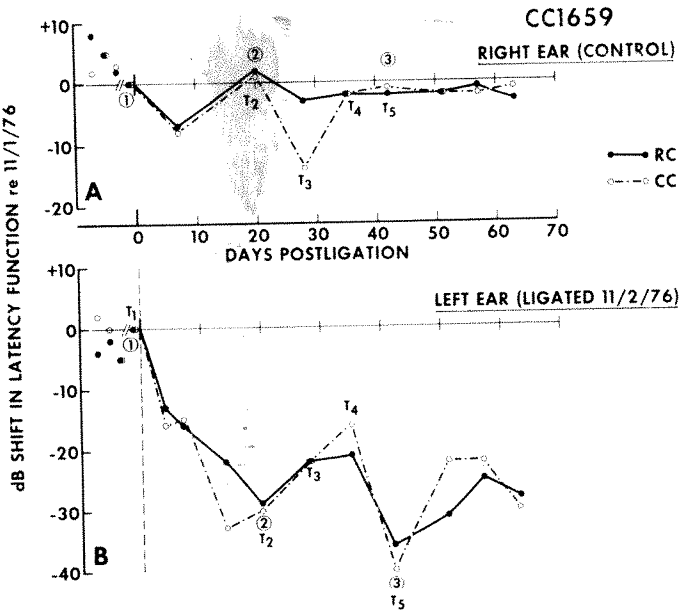

Fig. 3. Shift in latency functions for rarefaction (RC) and condensation (CC) clicks after ligation of the left ET of CC 1659. Shifts are all relative to preoperative control latency functions (points labeled 1 for each ear). Points to the left of day 0 are earlier preoperative controls. Points labeled 1, 2, and 3 correspond to level series 1, 2, and 3 of Fig. 1. Points labeled T_1 to T_5 correspond to recordings made immediately after tympanograms with same labels in Fig. 7.

RESULTS

Figure 1 depicts the amplitudes and latencies of N_1 responses from three recording sessions in both ears of CC 1659 both before and after ligation of the left ET. The response curves labeled 2 and 3 were obtained three and seven weeks postligation, respectively. It is apparent that both the amplitudes and latencies of responses at the same sound pressures remain relatively stable in the control (right) ear. However, the curves for N_1 latency in the ligated ear shift following ligation. The same trend is seen in the N_1 amplitude curves for most click levels, although for amplitude there is considerable crossing of the postoperative curves at high levels.

CC 1665 (Fig. 2) exhibited similar although smaller shifts in its latency curves, but demonstrated greater variation in the amplitude changes after ligation. Despite a progressive increase in the N_1 latency for the same level of clicks, at three weeks postligation (curve 3), the N_1 amplitudes at the highest click levels were more than twice those recorded preoperatively (see Discussion).

From Figures 1 and 2 it can be seen that postoperatively, the N_1 latency-vs-click level curves shift progressively to higher levels, whereas the change in N_1 amplitude is rather erratic. In our normal population of cats we also noted that N_1 latency was much more consistent than amplitude.[6] This was true both for the animals taken as a group and for the individual animal during various recording sessions. Therefore, we have taken the average shift in the N_1 latency-vs-click level functions as a measure of apparent hearing loss induced after ET ligation. At high click levels, latency changes little with changes in level. Consequently, responses with latency less than 1.3 msec for CCs or 1.1 msec for RCs were not included in the measurement of average shift. Since responses with very long latencies were usually of small amplitude and thus less reliable than those of larger amplitude,

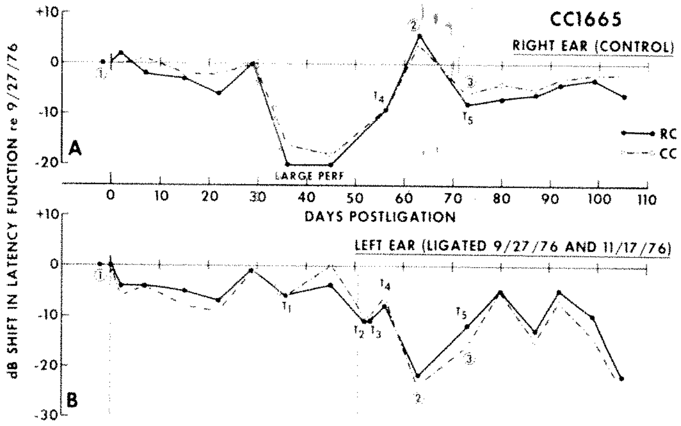

Fig. 4. Shift in latency functions for CC 1665 similar to Fig. 3. Left ET was ligated at day 0 with very little hearing loss ensuing. Left ET was religated and severed on day 51, resulting in a hearing loss (see text). Points labeled 1, 2, and 3 correspond to level series with same labels in Fig. 2. Points labeled T_1 to T_5 correspond to tympanograms with same labels in Fig. 8. The large loss on days 35 and 45 in the control (right) ear were due to a large perforation of the right TM.

the portions of the curves for latencies greater than 2 msec were likewise excluded from the measurement of average shift. Thus the dB shift in latency function described in subsequent figures is the average shift for latencies between 1.1 and 2 msec for RCs and between 1.3 and 2 msec for CCs. The shifts in Figures 3 to 6 are all plotted relative to a preoperative control for that ear.

All four animals demonstrated an early shift in latency function for both CCs and RCs. Shifts for the ligated ears of CC 1659, CC 1675, and AC 18 (Figs. 3, 5, and 6, respectively) reached a maximum of 15 to 35 dB at approximately 20 days postligation and then fluctuated over the ensuing 30 days. The shifts appeared to stabilize after 60 days (Figs. 5 and 6). CC 1665 (Fig. 4) demonstrated no significant shift in its

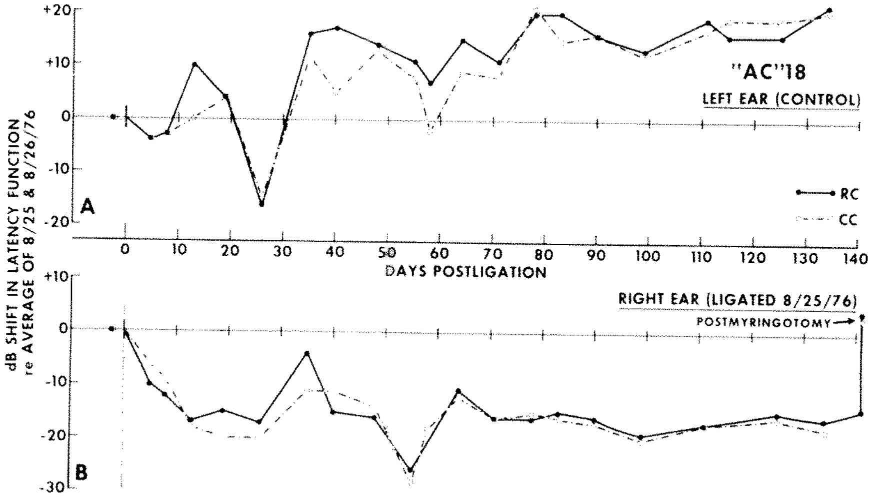

Fig. 5. Shift in latency functions for AC 18, similar to Fig. 3, following ligation of the right ET. Isolated recording indicating a loss, such as that of the control ear on day 26, probably resulted from improper insertion of the earbar into the auditory canal.

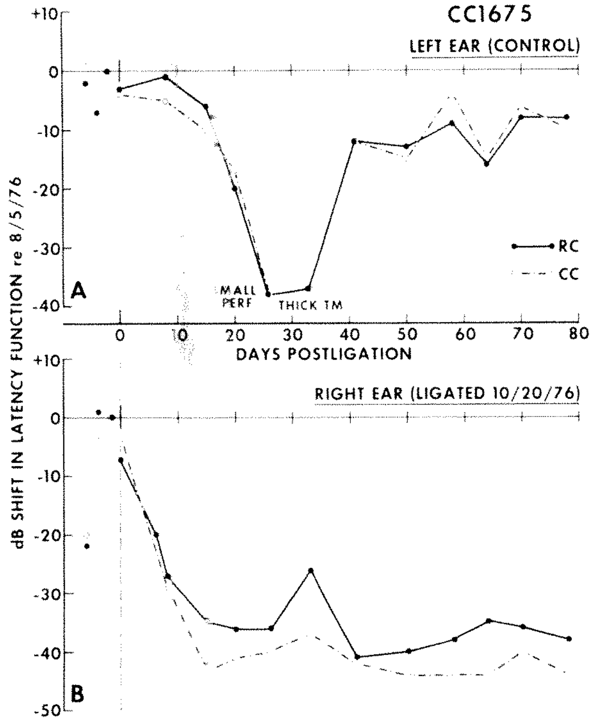

Fig. 6. Shift in latency function for CC 1675, similar to Fig. 3, after ligation of the right ET. The large loss on days 20 to 33 in the control (left) ear was due to a perforation of the left TM and subsequent thickening of the TM as this healed.

latency function during a 50-day period following ET ligation. On the 51st day the left ET was reexplored and the ligature was found to have loosened (See Methods and Materials). After religation and division of the ET, a 20 dB shift in the latency function was achieved by the 13th postoperative day.

Several of the control ears demonstrated apparent losses attributable to TM perforation which occurred during cleaning of the external auditory canals. CC 1665 (Fig. 4) sustained a large perforation of the right TM on day 35 which did not heal until day 56. Likewise, on day 27, CC 1675 (Fig. 6) was noted to have a small perforation of the left TM and a thickened TM on day 34. AC 18 (Fig. 5) demonstrated progressive hearing improvement in the control ear following ET ligation of the opposite ear. This animal underwent only one preoperative control session, and this was performed shortly after the meatoplasty. At the time of this control session, otitis externa of the control ear was noted, which was felt to account for attenuation of sound reaching the TM. As the inflammation of the control ear subsided, the hearing returned to the normal range for our cat population.

One hundred-forty days following ligation of the right ET of AC 18, a myringotomy was performed on the operated ear, with release of mucoid middle ear effusion. The premyringotomy latency shift corresponded to a 14 dB loss which immediately reverted to a 4 dB improvement over the preoperative measurements as determined by postmyringotomy recording on the same day (Fig. 5). Within three days, however, the TM had healed, fluid had reaccumulated in the middle ear space, and the latency shift corresponded to a 15 dB loss.

In addition to the ECochG changes following ET ligation, the presence of negative pressure or fluid formation was

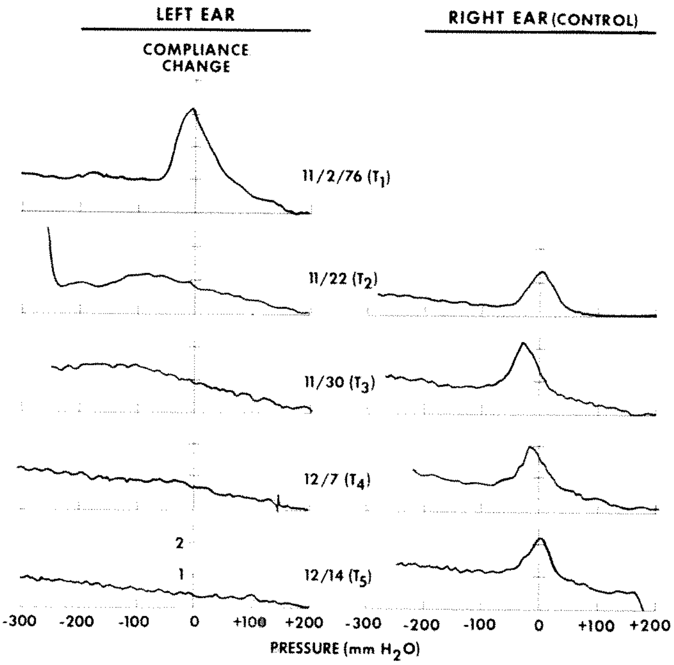

Fig. 7. Tympanograms before (T_1) and after (T_2 to T_5) ligation of the left ET of CC 1659. The hearing losses associated with these tympanograms are indicated by points T_1 to T_5 in Fig. 3.

indicated by serial tympanograms performed on the animals immediately prior to each recording. Figures 7 and 8 depict serial tympanograms for two of the animals used in this study. Tympanogram T_1 of Figure 7 represents the preligation control for the left ear of CC 1659. The pattern is that of a Type A (normal) response, according to the classification of Jerger.[7] Tympanograms

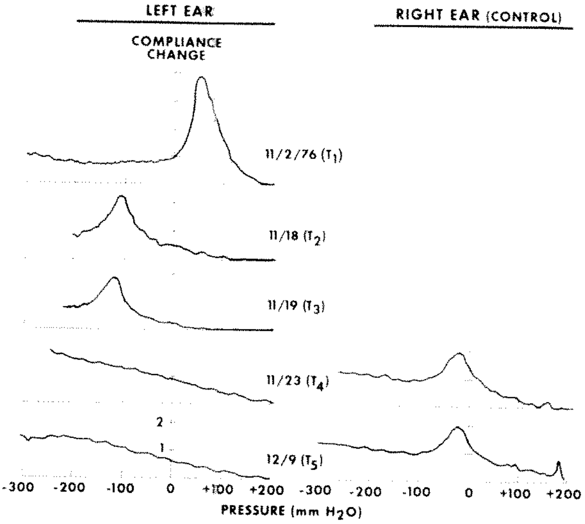

Fig. 8. Tympanograms before (T_1) and after (T_2 to T_5) ligation of the left ET in CC 1665 (second ligation; see text and caption of Fig. 4).

T_2 to T_5, representing days 20 to 42 postligation for the left ear, are Type B patterns; they indicate the presence of middle ear fluid. Note that the unoperated (right) ear maintains normal tympanograms throughout the series.

Figure 8 demonstrates serial progression from Type A (T_1) through Type C (T_2 and T_3), indicating negative middle ear pressure to Type B (T_4 and T_5). The patterns depicted are those obtained following religation of the left ET in CC 1665. Pattern T_2 (one day postligation) represents a negative middle ear pressure of 110 mm H_2O, while T_3 (two days postligation) represents a negative pressure of 120 mm H_2O. The presence of fluid in this animal is indicated by T_4 (Type B), and occurs by six days postligation.

The control ears retained normal (Type A) tympanograms throughout the testing periods. Only during the times of TM perforation did the control ears convert temporarily to a Type B pattern. A Type B pattern was also noted in AC 18 following removal of middle ear fluid. All the control ears which sustained TM perforations reverted to Type A tympanograms upon healing of the perforation.

DISCUSSION

The data presented here confirm that middle ear effusions can be produced by sterile ligation of the ET in the cat as first shown by Proud.[4] The consistent latency shifts observed here demonstrate that the closed system we have used for acoustic stimulation and auditory nerve recording can indeed detect a decrement in cochlear function induced by middle ear effusions.

In the preceding paper we concluded that N_1 latency was a more consistent measure of response than is amplitude. This conclusion is also reached on the basis of the data of Figures 1 and 2. In fact, on a number of occasions, ears which had developed middle ear effusions elicited responses of larger amplitude than they had prior to ligation, although their latency functions indicated a hearing loss. This is probably due to the fluid itself acting as an electrode and improving the electrical coupling from the cochlea to the external ear canal where responses were recorded. Thus the responses generated in the cochlea could have been reduced by the fluid, but our ability to record that response in the canal was enhanced, resulting in an increased amplitude at the recording electrode. Since such changes in amplitude should not appreciably affect the time-course of the response, the latency remains a valid measure.

The data of Figures 3, 5, and 6 indicate that after initial ET ligation, the shift in latency is progressive over the first 20 days. All cats showed some temporary improvement in their latency functions between days 30 and 40 postligation. The cause of this relief is not known at this time, but it may correspond to changes in the physical characteristics of the middle ear fluid or to an occasional air bubble sometimes seen in the early stages of effusion. In the two cats followed for the longest period after ligation, the losses stabilized between 40 and 60 days. The stabilized losses for these were approximately 15 dB for AC 18 (Fig. 5) and 40 dB for CC 1675 (Fig. 6).

Although at this stage we cannot explain the pathophysiology of the losses, the techniques described allow us to measure a decrement in cochlear function and to document its time-course.

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FAMILIAL DYSAUTONOMIA (RILEY-DAY SYNDROME)
TEMPORAL BONE FINDINGS
and
OTOLARYNGOLOGICAL MANIFESTATIONS

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FAMILIAL DYSAUTONOMIA (RILEY-DAY SYNDROME)

TEMPORAL BONE FINDINGS AND OTOLARYNGOLOGICAL MANIFESTATIONS

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SUMMARY — Familial dysautonomia, or Riley-Day syndrome, is inherited in an autosomal recessive fashion and occurs almost exclusively in Jewish families. This disorder is characterized by a smooth tongue devoid of fungiform papillae and of taste buds, and is clinically associated with poor taste discrimination. An unsteady gait and dizziness on change in position are also common presenting symptoms. This study reports the histopathological findings of eight temporal bones from four patients with documented familial dysautonomia. For the control series, 13 normal temporal bones were also studied. The most striking finding in the dysautonomic patients was an extreme paucity of geniculate ganglion cells ($P < 0.001$). A statistically significant reduction in the number of neurons was also found both in the superior and in the inferior divisions of the vestibular nerve ($P < 0.001$). The paucity of the geniculate ganglion cells correlates well with the impairment of the taste in dysautonomic individuals, since the afferent fibers leaving taste buds of the anterior two-thirds of the tongue run via the chorda tympani and have their cell bodies in the geniculate ganglion. Furthermore, the reduction in the number of Scarpa's ganglion cells observed in the dysautonomic patients studied here could account for a poor response to caloric test, positional vertigo and an unsteady gait in this condition.

INTRODUCTION

Familial dysautonomia (FD) was originally described by Riley et al[1] in 1949. The disorder appears to be of genetic origin transmitted as an autosomal recessive trait and occurs almost exclusively in Jewish families. It is characterized by markedly decreased taste discrimination caused by an absence of the fungiform papillae. The most common complaints are limitations in exercise tolerance and dizziness on change in position. An unsteady gait is also easily detected when the patient turns quickly.[2] In addition, an absence or marked diminution of lacrimination, diminished pain sensation, crises of vomiting, dysphagia, cutaneous blotching and excessive sweating are common.

Kelemen[3] reported a case of aural histopathology in familial dysautonomia in which he noted a dilatation of the osseous vestibular aqueduct. No other temporal bone findings in this disorder have been described to our knowledge. Recent pathologic studies on patients with FD revealed a reduction in the number of neurons in the cervical and thoracic sympathetic ganglia.[4] It has also been observed that the sural nerve, which is primarily sensory in function, has reduced transverse fascicular area and diminished number of axons in patients with FD.[5] If the deficiency of the sensory ganglion of dysautonomic individuals were generalized, one might expect an involvement of other neurons of special sensibilities within the temporal bones of patients with FD. Dizziness on change in position and a reduced response to caloric test in dysautonomic children reported by Axelrod et al[2] are suggestive of vestibular pathology. Furthermore, the taste impairment of dysautonomic patients could be related to a possible defect in the pathway of sense of taste in its course in the temporal bone, since the afferent fibers leaving the taste buds of the anterior two-thirds of the tongue run via the chorda tympani and have their cell bodies in the geniculate ganglion. Accordingly, the temporal bones from dys-

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autonomic patients were investigated with emphasis on the geniculate ganglion cells and on the Scarpa's ganglion cells.

The purpose of this study was, first, to determine whether there would be an involvement of neurons of special sensibilities within the temporal bones from dysautonomic individuals, and second, to provide an objective study of both geniculate and Scarpa's ganglion cells, and third, to describe clinical manifestations of the disorder.

METHODS AND MATERIALS

Eight temporal bones from four patients with documented FD were studied. For the control series, 13 temporal bones from nine individuals of approximately the same age and sex as the dysautonomic patients and those with no significant history of ear disease or neurologic disorder were selected.

They were decalcified, dehydrated and embedded in celloidin. Serial sections were cut at 22μ and were stained with Harris' H & E. Both geniculate and Scarpa's ganglion cells of the dysautonomic patients were counted and compared with counts made on control temporal bones. In counting the cells of geniculate ganglia every other section was stained with Mallory. The cell counts were made by counting the distinct nuclei present in the section and the total number was obtained by multiplying the sum by two as per the method described by Van Buskirk.[6] In the case of Scarpa's ganglia every tenth section was also stained with Mallory and the cells in both the superior and inferior vestibular nerves were counted and the total multiplied by ten.[7]

RESULTS

In the control series the number of the cells studied in 13 geniculate ganglia ranged from 2,164 to 4,830 with an average of 3,522 (Table 1). Van Buskirk[6] reported a range of 1,462 to 3,682 with an average of 2,169 in 12 ganglia of normal human subjects. His range and average are both below those found in this series.

In dysautonomic patients studied here, the number of the geniculate ganglion cells was strikingly reduced (Table 1) as compared to those of the controls.

In the control series the number of Scarpa's ganglion cells in the superior vestibular nerve ranged from 7,450 to 9,970 with a mean value of 8,796, while those in the inferior vestibular nerve ranged from 8,260 to 14,160 with a mean of 10,836. The total number for both divisions ranged from 14,480 to 24,110 with a mean value of 19,632 (Tables 2 and 4). These values are in agreement with those reported by Naufal and Schuknecht.[7] They counted the number of Scarpa's ganglion cells in 15 normal human specimens and reported a range of 6,000 to 10,680 with an average of 8,025 in the superior division. They also found the average number of cells in the inferior division to be 10,414 with the range of 8,260 to 14,050 and the average of the total number of both divisions to be 18,439 with the range of 14,920 to 22,390.

In the dysautonomic individuals studied here, the Scarpa's ganglia con-

TABLE 1. AVERAGE CELL COUNTS OF GENICULATE GANGLION

A. Controls: *Cases*	*No. of Cells*
1	3463
2	2753
3	4041
4	3295
5	2164
6	3464
7	4830
8	3370
9	4320
Avg.	3522.22
S.D.	801.10
S.E.	267.03
C/V	22.7 %
B. Dysautonomia: *Cases*	*No. of Cells*
1	183
2	48
3	201
4	401
Avg.	208.50
S.D.	145.96
S.E.	72.98
C/V	70.0 %

TABLE 2. AVERAGE CELL COUNTS OF SCARPA'S GANGLION

A. Controls:

Cases	*Age*	*Sup Div.*	*Inf. Div.*	*Total*
1	2.5	9805	12805	22610
2	18	6860	8865	15725
3	30	9555	11140	20695
4	1.5	9475	10420	19895
5	2.5	9740	13400	23140
6	4	9210	9720	18930
7	10	8070	13500	21570
8	0.5	9000	8710	17710
9	50	7450	8960	16410
Avg.	13.22	8796.11	10835.56	19631.67
S.D.	16.89	1075.07	1967.96	2644.86
S.E.	5.63	358.36	655.99	881.62

B. Dysautonomia:

Cases	*Age*	*Sup Div.*	*Inf. Div.*	*Total*
1	3.5	4345	5355	9700
2	16	3870	4055	7925
3	2	4850	4980	9830
4	30	3200	3340	6540
Avg.	12.88	4066.25	4432.50	8498.75
S.D.	13.02	702.58	910.46	1568.56
S.E.	6.51	351.29	455.23	784.28

tained considerably fewer cells (Tables 2 and 4) than those of the control series.

Data were analyzed statistically to determine whether or not there was a significant reduction both in the number of the geniculate ganglion cells and in the number of the Scarpa's ganglion cells.

Analysis of Geniculate Ganglion Cells. The counts are recorded for some subjects in terms of right and left values, while for others only a right or left, respectively, is available. Consequently, in the analysis, examinations are made of whether or not any significant differences exist between right and left values. Furthermore, computations of mean and standard deviations are done separately for those individuals with bilateral counts and those with unilateral counts. For the controls, the differences of right and left are nonsignificant ($0.7 > P > 0.6$). A corresponding calculation was made for the dysautonomic patients; here again right and left differences are not significant ($0.5 > P > 0.4$). Based on these findings, the patients with unilateral counts and the controls with unilateral counts will be treated together with those having bilateral counts. The average of right and left count is used for those individuals with bilateral counts. Table 1A presents all the results for the controls, averaging bilateral counts, and Table 1B shows all the results for the dysautonomic patients, also averaging bilateral counts, as described. A test of the mean differences between the controls and the patients with dysautonomia may now be undertaken.

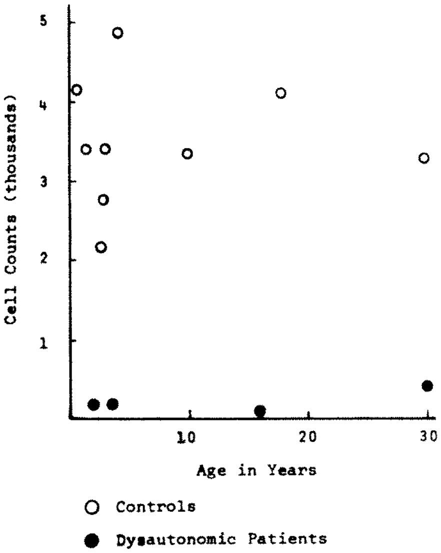

Fig. 1. Plot of age and cell counts of geniculate ganglion cells: controls vs dysautonomia.

Figure 1 shows the plot of age and cell counts for both controls and dysautonomic patients. The correlation coefficients have been calculated in each case and the results ($r_1 = 0.02$, $P > 0.1$; $r_2 = 0.55$, $P > 0.1$, respectively) show no significant age vs cell count relationship. It should be pointed out, however, that the correlation coefficient for the patients with dysautonomia is a suggestive one (although nonsignificant), while that for the controls shows no suggestion of age dependency whatsoever. As seen in Table 1, not only does a rather dramatic difference exist between mean results of cell counts, but there is a dramatic difference in the standard deviations of each group as well. A variation ratio test (F^{8}_{3} = 28.54, $0.05 > P > 0.01$) confirms a significant disparity in the standard deviations and hence we must conclude that heterogeneity is present between the two groups. For that reason, the *t*-test of mean difference must be carried out in a special way: $t = \frac{(\text{Avg. } 1 - \text{Avg. } 2)}{(\text{SE}_1)^2 + (\text{SE}_2)^{2 \cdot 1/2}} = 11.97$, $P < 0.001$. By comparison of this result to a "*t*" ratio constructed in a weighted fashion to take account of heterogeneity,[8] it is found that the result is a highly significant one. Hence, testing the cell counts of the dysautonomic patients against those of the controls has elicited two sets of significant findings: 1) the dysautonomic patients show significantly smaller mean cell counts of the geniculate ganglion than the controls do; 2) the dysautonomic individuals show significantly smaller standard deviations or significantly smaller spread of cell counts than the controls do.

Analysis of Scarpa's Ganglion Cells. There are three values available for the analysis of the vestibular ganglion cells. These are the cell counts of the superior division, of the inferior division and of the total counts of the two added together. Consequently, computations are done separately for each of these three parameters.

Once again some subjects have both right and left cell counts, while others have either a right or left value alone. As previously described, an examination was made to determine whether or not there were significant differences between right and left cell counts. Furthermore, computations of mean and standard deviation are done for the counts of the superior division, of the inferior division and of the total separately. The findings indicate that there are no significant differences between right and left cell counts in the controls. In the dysautonomic patients, the differences between right and left cell counts are also not significant. Therefore, it is possible to treat the cases of dysautonomia with unilateral counts and the controls with unilateral counts together with those having bilateral counts. Table 2 presents all the results both for the controls and for the dysautonomic patients, averaging bilateral counts, as described. This table will be used for further analysis of the data.

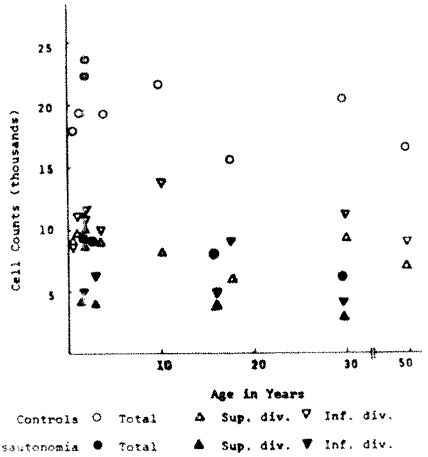

Fig. 2. Plot of age and cell counts of Scarpa's ganglion cells: controls vs dysautonomia.

Figure 2 depicts the age-cell count relationship for both the control series and for the dysautonomic patients. The correlation coefficients have been calculated and the results are shown in Table 3. In the dysautonomic patients

TABLE 3. AGE CORRELATIONS OF SCARPA'S GANGLION CELLS

	Sup. Div.	*Inf. Div.*	*Total*
Controls	$r_7 = -0.54$ $P > 0.1$	$r_7 = -0.33$ $P > 0.1$	$r_7 = -0.47$ $P > 0.1$
Dysautonomia	$r_2 = -0.97$ $0.05 > P > 0.02$	$r_2 = -0.97$ $0.05 > P > 0.02$	$r_2 = -1.00$ $0.01 > P > 0.001$

TABLE 4. SUMMARY OF ANALYSIS OF COVARIANCE CONTROLS VS DYSAUTONOMIC PATIENTS

	Sup. Div.	*Inf. Div.*	*Total*
Heterogeneity	$F^7_2 = 20.02$ $P > 0.05$	$F^7_2 = 52.34$ $0.05 > P > 0.01$	$F^7_2 = 225.76$ $P < 0.01$
Differences between slopes △ cells /△ ages	$F^1_9 = 0.18$ $P > 0.1$	$F^1_9 = 0.11$ $P > 0.1$	$F^1_9 = 0.19$ $P > 0.1$
Differences between adjusted avg.	$F^1_{10} = 92.51$ $P < 0.001$	$F^1_{10} = 40.64$ $P < 0.001$	$F^1_{10} = 77.24$ $P < 0.001$

there is a significant relationship between the age and the cell counts for the superior division, the inferior division and the total. However, in the control series no significant relationships are noted between the age and the cell counts.

In the analysis between the controls and the dysautonomic patients, the age correlation of the dysautonomic patients must be taken into account by a covariant analysis. Table 4 summarizes the analyses of covariance. These analyses compare the linear relationships shown in Figure 2, which are expressed as correlations in Table 3. These analyses take into account the age effect, when present, in any one of the groups being compared.

It is observed that for the counts of the inferior division and for the total cell counts, the age relationship of these cell counts for the dysautonomic patients is more predictable or more uniform than the age relationship of the cell counts for the controls (see significant heterogeneity findings in Table 4). This tendency is also observed for the cell counts of the superior division, but the finding here is not a significant one. No findings of significant differences between the controls and the dysautonomic patients of "decrement of cells per increment of age" are seen for the superior, the inferior and the total cell counts (see Table 4, differences between slopes). However, for each of the parameters, the total, the superior and the inferior cell counts, there is found for comparable ages a significantly lower number of cells in the dysautonomic patients than in the controls (see Table 4, adjusted averages). The average age of this group of patients and controls is 13.1 years and the age adjusted significant differences between the dysautonomic patients and the controls are summarized in Table 5 for this average age.

CASE REPORTS

Case 1

This was a female child of Jewish extraction, first seen at the age of ten months because of breath holding spells, poor suck and recurrent episodes of vomiting. The mother noted that the baby was unable to shed tears. Diagnosis of familial dysautonomia was made by a histamine test at the age of ten months. She weighed 7.2 kg at one year of age, walked unsteadily and her skin blotched easily. A fracture of the metatarsus of the right foot went unnoticed because of her sensory deficit. Her hearing seemed normal. She was admitted to New York University Medical Center at the age of two because of pneumonia. Physical examination at that time showed the child to be in moderate respiratory distress. There was wheezing in the chest with poor aeration. The right tympanic membrane was perforated and a serous discharge was present. The left ear was normal. The tongue was unusually smooth on the dorsal surface. Deep tendon reflexes were absent. Only occasional response was

TABLE 5. AGE ADJUSTED CELL COUNTS OF SCARPA'S GANGLION

	Sup. Div.	*Inf. Div.*	*Total*
Controls: Age adjusted average	8800	10840	19640
Dysautonomia: Age adjusted average	4057	4422	8479
Differences: Age adjusted average	4743	6418	11161

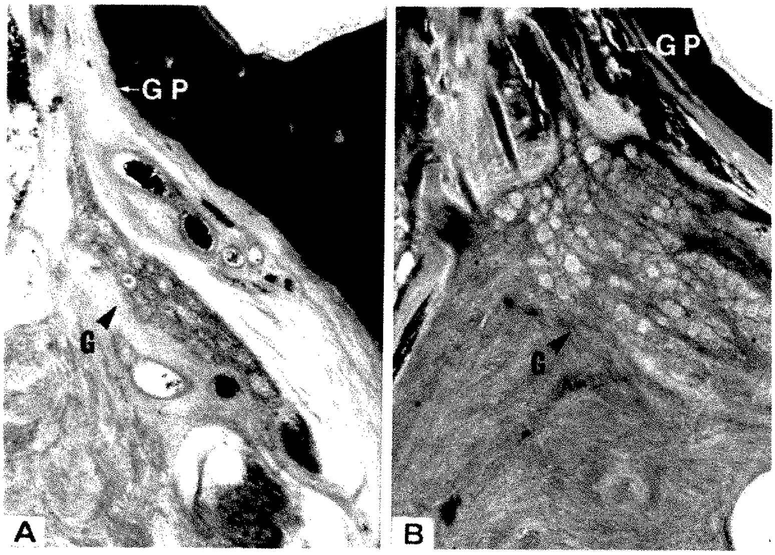

Fig. 3. Geniculate ganglion contains fewer neurons in dysautonomic patient (A) than that of the control (B). G - Geniculate ganglion cells; GP - Greater petrosal nerve. (Mallory, X 64)

elicited by pin pricks. Chest x-ray showed an extensive pneumonia that was presumed to be caused by vomiting and aspiration. Following her recovery from pneumonia she was sent home and did fairly well until 3½ years of age when she developed choking spells, vomiting and aspiraton. On her way to the hospital respiratory arrest occurred and she was dead on arrival. The autopsy was performed three hours postmortem. The findings were aspiration pneumonia, a smooth tongue with no evidence of fungiform papillae and cyanotic buccal mucosa. A microscopic study of the tongue showed an unusually small number of taste buds. Both the pharynx and larynx were normal. The cervical sympathetic chain contained fewer than the usual number of neurons. In addition, the sural nerve was noted to be atrophic. The temporal bones were removed three hours after death and were processed in the usual manner.

Right Temporal Bone.

EXTERNAL AND MIDDLE EAR. The external auditory canal was normal. The middle ear cleft and the mastoid cavity were lined with a thick and edematous mucosa with infiltration of inflammatory cells. The malleus, incus and stapes were all normal.

INNER EAR. The organ of Corti was well-developed and the hair cells were present. The vestibular maculae and cristae appeared to be fully developed and the hair cells were present. The endolymphatic duct and sac were normal.

NERVE AND GANGLION. Tissue preservation was excellent, allowing for a good interpretation of nerve and ganglion cells. The facial nerve ran its normal course. The geniculate ganglion contained strikingly few cells (Fig. 3A), as previously described. The chorda tympani appeared to be small in diameter. The Scarpa's ganglion cells were considerably reduced in number (Fig. 4A), the reduction being both in the superior and inferior divisions as previously mentioned. The number of cochlear neurons also seemed to be reduced.

Left Temporal Bone. Findings on the left ear were essentially similar to those on the right.

Case 2

This was a 16-year-old boy of Hebrew extraction who was diagnosed as having familial dysautonomia as a child. He had a history of multiple hospitalizations for pneumonia which was associated with vomiting and aspiration, on one occasion requiring a tracheostomy. Several episodes of vomiting occurred while he was a passenger in an automobile. He was taken to the local hospital, where he was found to be in cardiorespiratory arrest. The patient remained in a coma despite attempts to resuscitate him. A large amount of the aspirated food and secretions were removed by bronchoscopy. On the second hospital day a tracheostomy had to be performed to permit effective suctioning and to place him on a respirator.

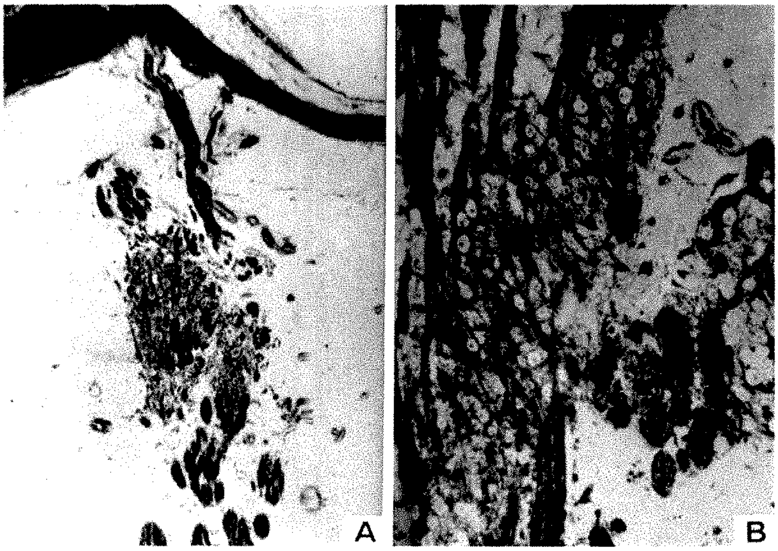

Fig. 4. Scarpa's ganglion cells are reduced in number in dysautonomia (A) compared with those of the control (B): both are superior vestibular ganglia. (Mallory, X 64)

Gradual deterioration occurred and on the fifth day his cardiorespiratory function ceased entirely. Autopsy was performed two hours postmortem. Pertinent findings were an extensive aspiration pneumonia, marked edema of the epiglottis and an unusually smooth and pale tongue. In addition, absence of the right olfactory bulb was noted. The temporal bones were removed at the time of the autopsy two hours after death.

Right Temporal Bone.

EXTERNAL AND MIDDLE EAR. The external auditory canal was normal. Middle ear cleft and mastoid cells were lined by a thick mucosa and contained an acidophilic fluid indicating serous otitis. The ossicles were all normal.

INNER EAR. The organ of Corti was well-developed and the hair cells were present. The vestibular maculae and cristae appeared to be well-developed. The hair cells of the end-organs were present. The endolymphatic duct and sac were normal.

NERVE AND GANGLION. The facial nerve ran its normal course. The chorda tympani was identified as it entered the iter chordae posterius passing through the tympanic cavity. The chorda tympani was small in diameter throughout its course in the temporal bone. The cross-sectional area of the chorda tympani in the iter chordae posterius (Fig. 5A) was compared with that of a ten-year-old boy (control) who died of skull fracture in an automobile accident (Fig. 5B). The cross-sectional area of the chorda tympani of this dysautonomic patient was not only smaller than that of the control, but also appeared to contain fewer nerve fibers (Fig. 5A, B).

The total number of the geniculate ganglion cells in this dysautonomic patient was only 50 (Table 1), while that of the control was 3,370. In addition to the reduction in the number of both the geniculate and the vestibular ganglion cells as previously described, the cochlear neurons also seemed to be fewer in number than those of the control (Fig. 6).

Left Temporal Bone. Pathological findings were similar to those on the right ear.

Case 3

This was a two-year-old boy born to Jewish parents. He was the product of breech delivery and weighed 7.4 kg at birth. The patient was evaluated at one month because of dry eyes, hypotonia and weak suck. His tongue was quite smooth and pale on the dorsal surface. Diagnosis of familial dysautonomia was made by positive histamine and Mecholyl® tests as well as by clinical manifestations. Lacrimation never occurred in this child. He developed a serious corneal ulcer and had to be hos-

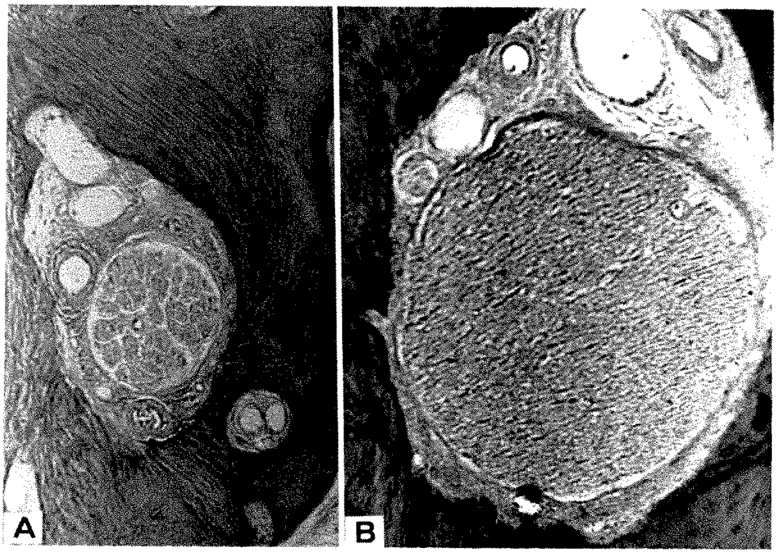

Fig. 5. Cross-sectional area of the chorda tympani nerve in the iter chordae posterius. (A) Dysautonomia; (B) Control. (H & E, X 80)

pitalized for removal of the corneal opacification when five months old. At that time a spontaneous nystagmus was noted on physical examination. The external ear canal and the tympanic membrane were normal on either side. The tongue was unusually smooth and pale. Pinpricks to the sole elicited withdrawal of the toe and foot, but no expression of pain such as grimace or cry was observed. Deep tendon reflexes were absent. The patient underwent a lamellar keratoplasty and his postoperative course was uneventful. Following discharge from the hospital the patient was well until the age of two when he was brought to the hospital with high fever, coughing and lethargic appearance. Chest x-ray on admission showed an extensive infiltration of the lung fields complicated by a mediastinal emphysema. Despite intensive treatment his respiratory status deteriorated and two episodes of cardiorespiratory arrests occurred during the course of the admission. After the second arrest he became comatose and a tracheostomy had to be employed to permit effective suc-

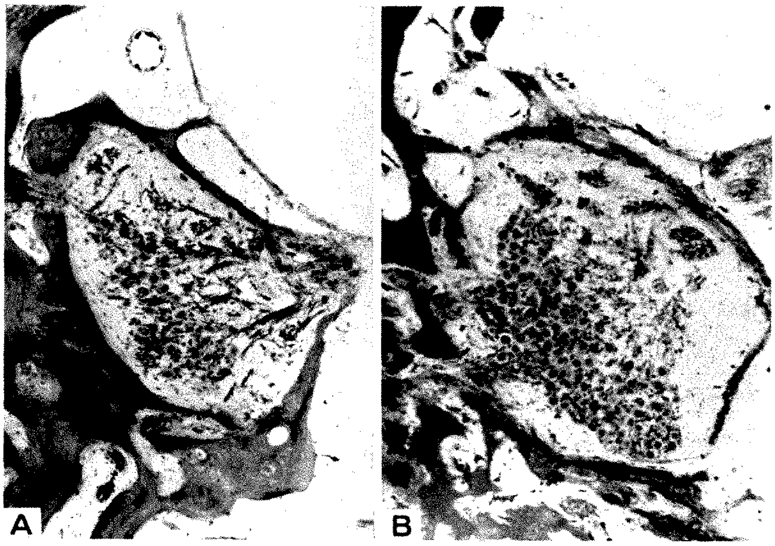

Fig. 6. Population of the cochlear neurons in dysautonomic patient (A) appears to be smaller than that of the control (B). (H & E, X 64)

tioning of the bronchial secretions and to place him on a respirator. The child expired on the eighth hospital day and autopsy was carried out 30 hours postmortem. Pertinent findings were: focal hemorrhage in both lungs, hemorrhage in the tracheobronchial tree and pneumomediastinum. The tongue showed a smooth and atrophic surface with diminished fungiform papillae. The temporal bones were removed at autopsy.

Right Temporal Bone.

EXTERNAL AND MIDDLE EAR. The external auditory canal was normal. The tympanic membrane was intact and the ossicles were normal. The middle ear cleft and mastoid cells were lined by a thick edematous mucosa with infiltration of lymphocytes, polymorphonuclear leukocytes and erythrocytes.

INNER EAR. The organ of Corti and vestibular neuroepithelia could not be fully evaluated because of postmortem autolysis.

NERVE AND GANGLION. The facial nerve appeared to be normal throughout its course in the temporal bone. The geniculate ganglion cells were well-preserved, allowing for an accurate counting of the cells. The number of the neurons within the geniculate ganglion was markedly reduced as previously described. The cross-sectional area of the chorda tympani was considerably smaller than that of the control specimen (a 2½-year-old crib death). The Scarpa's ganglion cells appeared to be reduced in number, but its cell counting could not be accurately done because of postmortem autolysis. The postmortem changes also affected the spiral ganglion cells.

Left Temporal Bone. Pathological findings were similar to those in the right ear with the following exceptions: collection of inflammatory cells were seen in the scala tympani, the internal meatus and the cochlear aqueduct, indicating suppurative labyrinthitis. All ganglion cells were better preserved than those of the right side. A reduction in the number of all neurons was again noted.

Case 4

This was a 30-year-old female with known familial dysautonomia who died of respiratory arrest at home. The temporal bones were removed two days after her death.

Right Temporal Bone. The external auditory canal and the tympanic membrane were not included in the specimen. The ossicles were all normal. The mucous membrane lining the middle ear and mastoid cells was also normal.

INNER EAR. The organ of Corti showed postmortem autolysis of the hair cells and a collapsed Reissner's membrane.

NERVE AND GANGLION. The facial nerve appeared to be normal. The chorda tympani was small in diameter. Both the geniculate and spiral ganglion cells had undergone postmortem autolysis. Thus, an evaluation of neuronal population of these ganglia could not be done satisfactorily. The Scarpa's ganglion cells, however, were well-preserved, allowing for an adequate cell count which showed a reduction in number as described.

Left Temporal Bone. Pathological findings were similar to those on the right with the following exceptions: both the geniculate and spiral ganglion cells were better preserved, allowing for estimations of the neuronal population. These neurons were reduced in number as previously described.

CLINICAL MANIFESTATIONS

Familial dysautonomia is a rare neural disorder which has many clinical abnormalities of interest to otolaryngologists.

Absence of Fungiform Papillae on the Tongue. This is the first consistent pathologic finding in dysautonomia.[9] The tip of the dysautonomic tongue is smooth and pale because of the clinical absence of vascularized fungiform papillae.[10] Smith and Dancis[11] found that taste perception and discrimination are deficient in patients with dysautonomia. The first three of our four cases had smooth and pale tongues; detailed information on Case 4 was not available.

Otologic Manifestations. Vestibular symptoms: It is reported by Axelrod et al[2] that the dysautonomic child commonly walks unsteadily, with a broad base, and that a few learn to ride a bicycle and that dizziness occurs on change in position, especially when the patient turns quickly. The cause of ataxia, they state, is probably a vestibular nerve deficiency, easily demonstrated by abnormal response to caloric test. Review of the clinical records of our four cases failed to document results of caloric tests or other neurotologic investigations. Hearing acuity: De Hirsh and Jansky[12] and later Halpern et al[13] examined the hearing of dysautonomic children and reported that all hearing levels tested were within the accepted range of normal. In our four cases, no evidence of hearing loss was recorded clinically or on the hearing test, although an evidence of serous otitis was noted on examination of the temporal bone.

Diminished Lacrimation. One of the most distinctive clinical signs in patients with familial dysautonomia is the absence or marked diminution of overflow tearing. The Schirmer test is reported to be subnormal and the lacrimal glands are histologically normal.[14] Poor lacrimation was noted in three of our four patients studied here.

Tracheobronchial Problems. Recurrent pneumonia is frequent and repeated aspiration is the major cause of pulmonary disease.[2] Tracheostomy is often necessary to permit a long-term removal of secretions, to prevent aspirations and to permit the use of a respirator. All the four patients presented here died of aspiration pneumonia with respiratory failure.

DISCUSSION

Geniculate Ganglion. For the sense of taste, the receptors are taste buds, located predominantly on the dorsal surface of the tongue. They are numerous on the sides of the circumvallate papillae and on the fungiform papillae. From the receptors of the anterior two-thirds of the tongue, taste fibers diverge to enter the chorda tympani via the lingual nerve. The cell bodies of the special visceral afferent from the anterior two-thirds of the tongue lie in the geniculate ganglion.[15] The greater petrosal nerve is a mixed nerve, containing parasympathetic and sensory fibers. The sensory fibers take their origin from cell bodies within the geniculate ganglion and are distributed to the soft palate through the lesser palatine nerve and anterior two-thirds of the tongue through the chorda tympani.

An extreme paucity of neurons within the geniculate ganglion, the most consistent histopathologic finding in all cases of dysautonomia studied here, would result in an interruption of the passage of impulses from the taste buds of the tongue via the chorda tympani nerve and also from the soft palate through the greater petrosal nerve. The finding correlates well with poor taste discrimination associated with dysautonomia.

Chorda Tympani. The chorda tympani contains afferent nerve fibers of taste and efferent parasympathetic secretomotor fibers traveling from the inferior salivary nucleus to the submandibular and sublingual glands. The majority of the fibers composing the chorda tympani nerve are special afferents for taste which have their cell bodies in the geniculate ganglion.[16] Foley[17] reported data on the ratio of sensory to preganglionic visceral motor fibers of the chorda tympani. The ratio of morphological types of axons was studied in cats and dogs. He found that sensory axons predominate in the chorda tympani of the dog, the ratio being two sensory axons for every motor nerve fiber. In the majority of instances, he observed that the sensory axons are also the most numerous functional type of nerve fibers in the chorda tympani of the cat. The cross-sectional area of the dysautonomic patients studied here was consistently smaller than those of the controls and the density of nerve fibers in the chorda tympani also appeared to be reduced in the dysautonomic patients. It is assumed, therefore, that an extreme paucity of neurons in the geniculate ganglion of dysautonomic patients is associated with fewer than the normal sensory fibers in the chorda tympani. Since the sensory fibers are predominant in the chorda tympani as described, the reduction in the sensorial component could account for a smaller cross-sectional area of the nerve. It is also possible that a similar defect would exist in the parasympathetic component of the chorda tympani of dysautonomic individuals. However, this would require further investigation.

Tongue and Taste. Pearson et al[18] reported that the fungiform papillae were present on the tongue of dysautonomic patients, but were rudimentary. He observed that there were no taste buds seen and that there presumably was a deficiency in sensory fibers in the submucosa of the tongue, providing an anatomical explanation for impaired taste discrimination characteristic of dysautonomia.

Taste buds are widely distributed over the tongue, but are mainly concentrated around the fungiform papillae and circumvallate papillae. These are visible projections of the tongue which account for the characteristic rough and uneven surface, and in their absence the tongue is pale and smooth.[10] When the sensory innervation of taste buds is experimentally sectioned, the buds degenerate and disappear.[19] Bull[20] studied 125 cases of patients follwing stapedectomy in which the chorda tympani was sectioned. His observation was that the fungiform papillae of the tongue showed atrophy, well-defined to the midline, following a section of one nerve, and the surface of the tongue became smooth and pale on the denervated side. It has been repeatedly demonstrated that the growth of nerve fibers into fungiform papillae precedes the appearance of the taste buds in their development.[21,22] Thus, the development of the taste buds appears to be dependent on the ingrowth of the nerve into the connective tissue core of the forming fungiform papillae and on the proper development of the fungiform papillae.[21] The hypoplasticity of the chorda tympani with few nerve fibers, observed in all of the dysautonomic patients presented here, suggests that a deficiency of the ingrowth of the nerve towards the fungiform papillae exists and that it results in a lack of formation of the taste buds subsequently. Furthermore, the deficiency of the nerve fibers might account for rudimentary fungiform papillae or an absence of the papillae characteristic of dysautonomia.

The extreme paucity of the neurons in the geniculate ganglion also suggests that there is a deficit in sensory impulses from the taste buds of the tongue to the central pathway via the geniculate ganglion, providing an explanation for the poor taste discrimination of dysautonomic individuals.

Vestibular Neurons. These were considerably reduced both in the superior and inferior divisions of the vestibular nerve in all dysautonomic patients studied here. The vestibular sensory epithelia appeared to be normal. It is, therefore, reasonable to assume that a vestibular pathway disorder resulting from a reduced number of the vestibular neurons accounts for a poor response to caloric test, dizziness on change in position, and an unsteady gait in dysautonomic patients.

Cochlear Neurons. In the dysautonomic patients presented here, the organ of Corti appeared to be normal, however, population of the spiral ganglion cells seemed to be reduced to some extent. A loss of population of the cochlear neurons in the presence of a functional end-organ creates a distinctive pattern of auditory dysfunction characterized by a loss of speech discrimination which is relatively more severe than the hearing loss for pure tone. Schuknecht and Woellner[23] found that up to 75% of cochlear nerve fibers were destroyed without creating a threshold elevation. He concluded that a small number of cochlear nerve fibers were adequate to conduct an impulse of threshold magnitude, but the greater number of nerve fibers were needed to conduct the complex neural pattern of speech. The hearing of dysautonomic children was reported to be within accepted range of normal hearing as previously described, yet a detailed study of speech discrimination in this disorder has not been reported in the literature. It appears that the number of cochlear neurons and of cochlear nerve fibers are adequate to conduct an impulse without creating an elevation in pure tone threshold in individuals with familial dysautonomia. However, further investigation is necessary in order to correlate the number of the cochlear neurons with the hair cells in patients with dysautonomia.

SUMMARY

1. The most striking finding in temporal bones of patients with familial dysautonomia is an extreme paucity of the geniculate ganglion cells.

2. The cross-sectional areas of the chorda tympani nerve of the dysautonomic patients are consistently smaller than those of controls.

3. The findings correlate well with the impaired taste discrimination and with the lack of formation of taste buds in the tongue of dysautonomic patients.

4. There are reductions in the number of the vestibular ganglion cells both in the superior and the inferior divisions. This accounts for vestibular manifestations of dysautonomic patients.

5. Population of the cochlear neurons appears to be below normal in dysautonomic patients.

6. In dysautonomic individuals, neurons of special sensibilities within the temporal bone are all involved.

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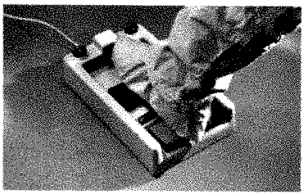
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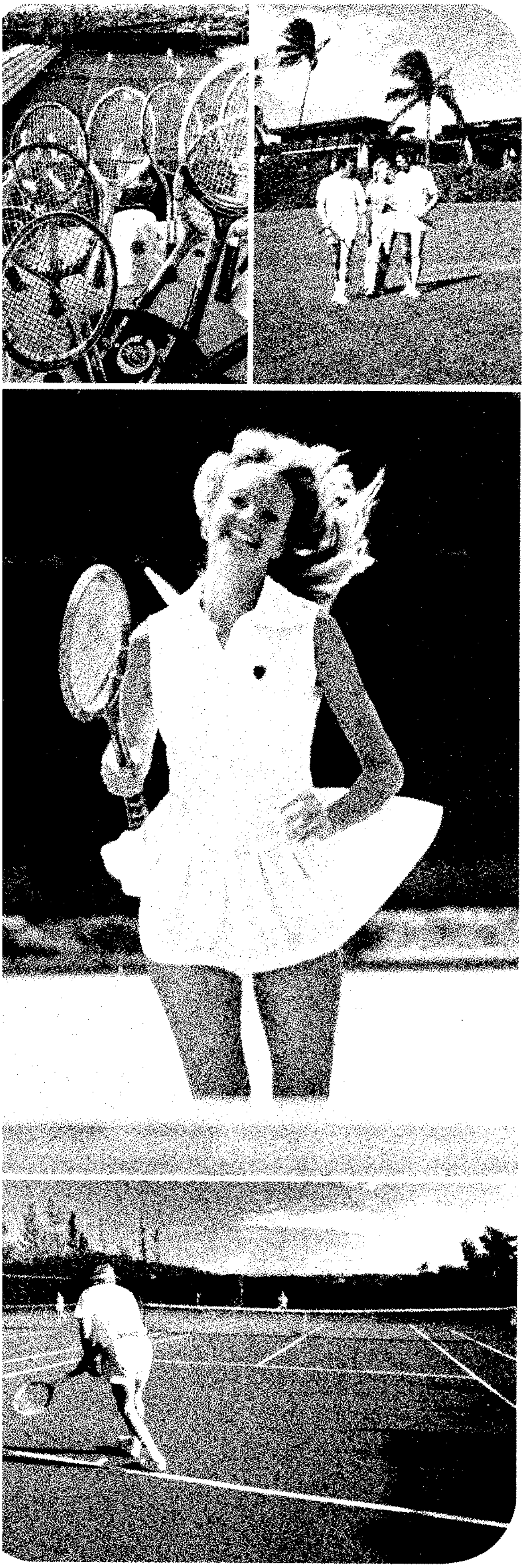

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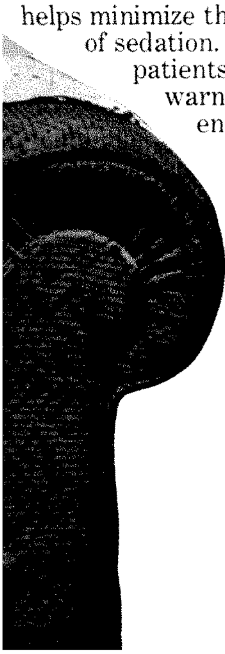

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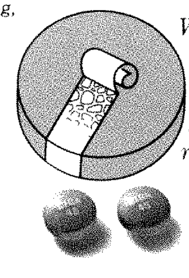

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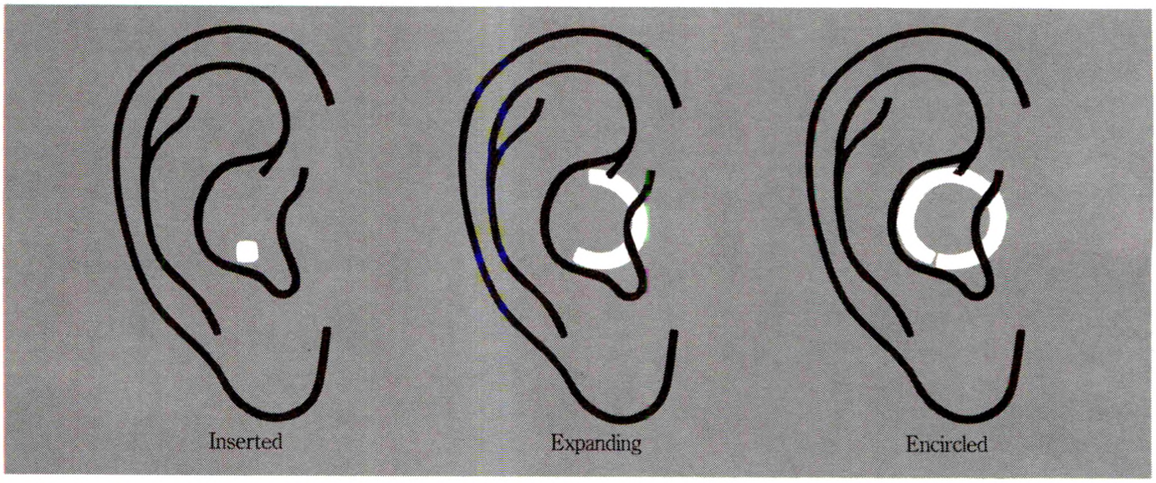

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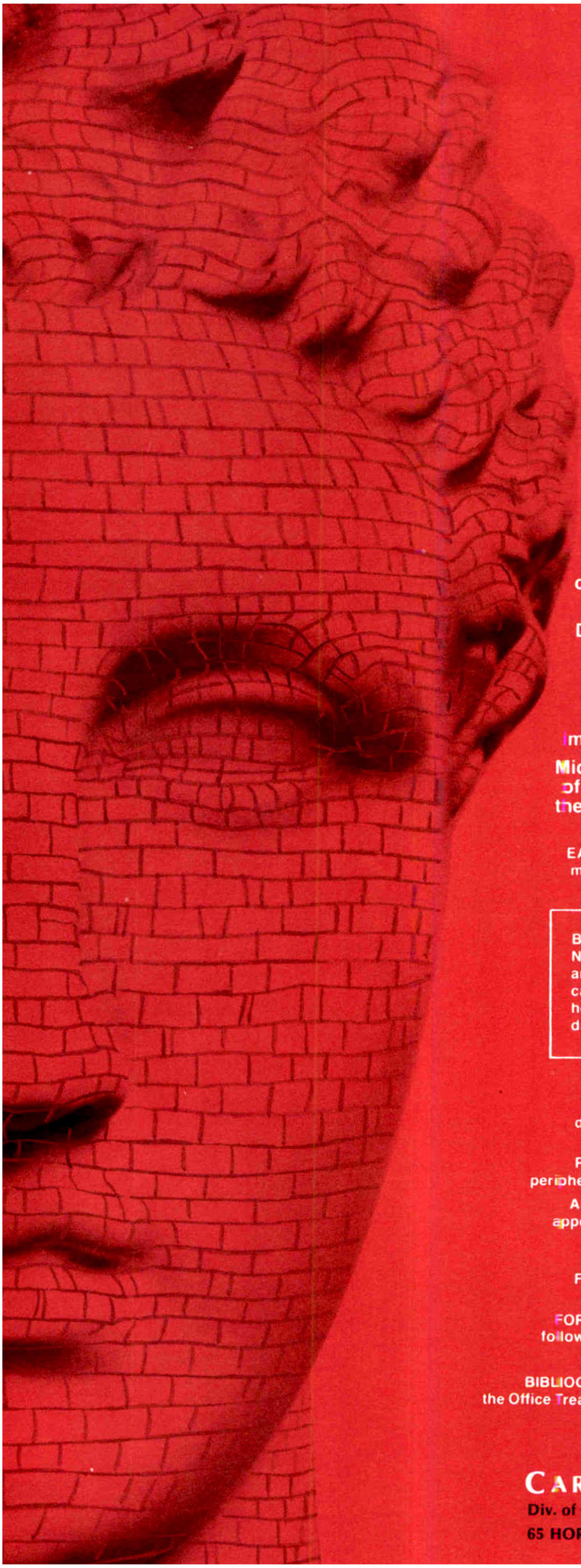

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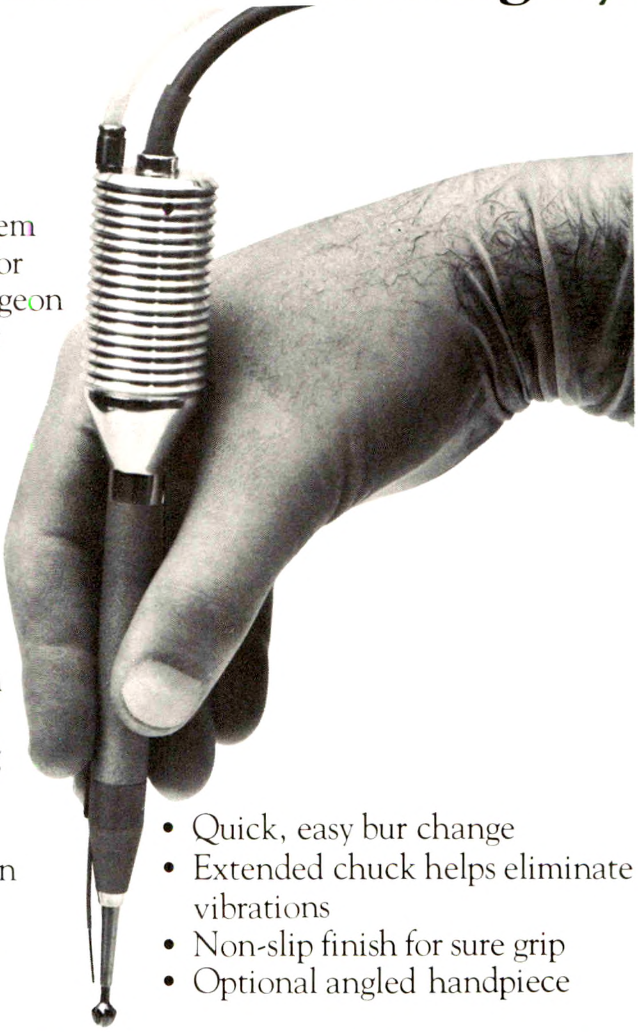

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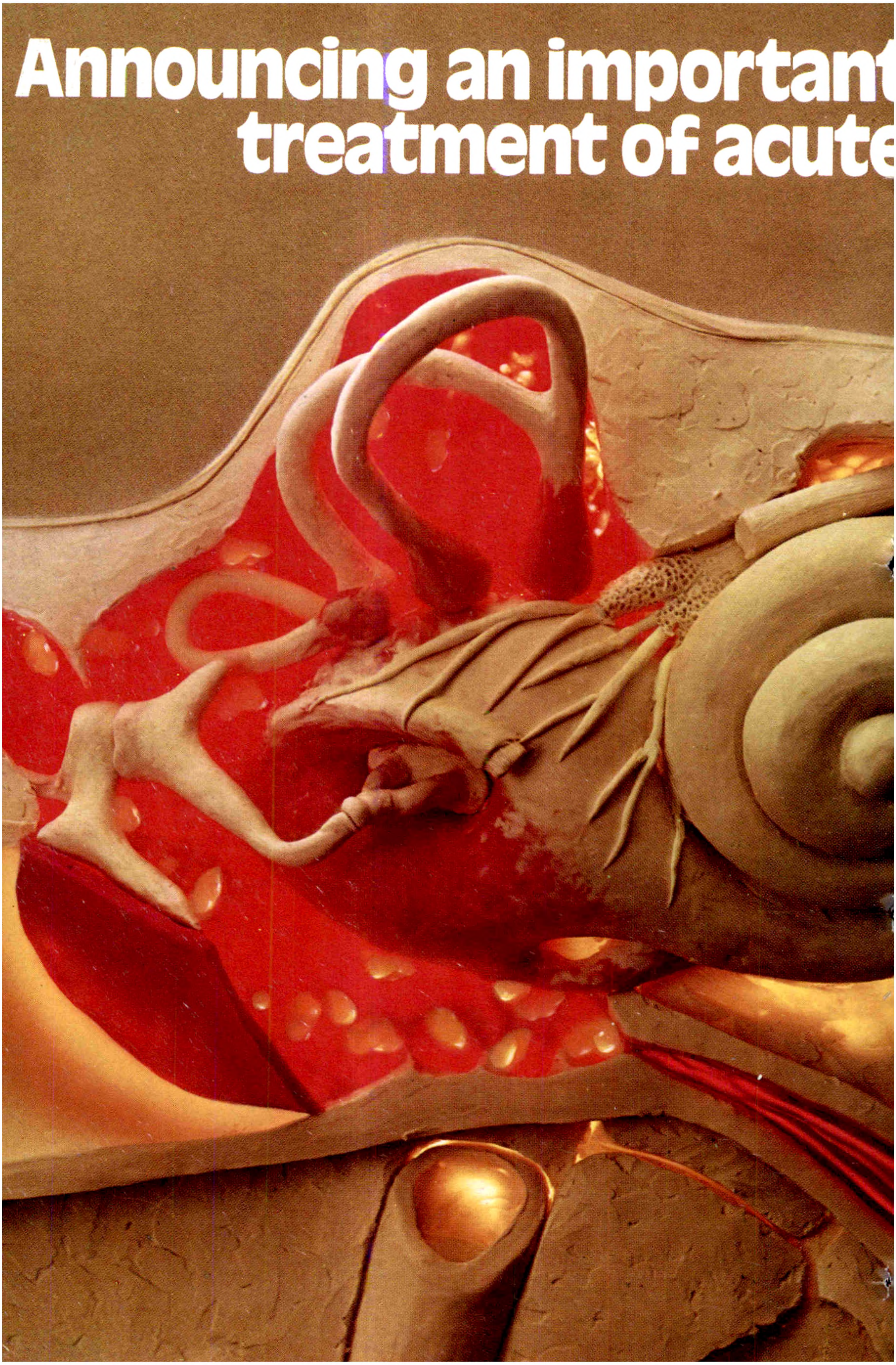
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(40 mg trimethoprim and 200 mg sulfamethoxazole per 5 ml)

Convenient b.i.d. therapy

Please see following page for summary of product information.

A major nonpenicillin now indicated
for acute otitis media in children

Bactrim™

Suspension Pleasant fruit-licorice flavor
Each teaspoonful (5 ml) contains
40 mg trimethoprim and 200 mg sulfamethoxazole.

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Each tablet contains 80 mg trimethoprim and
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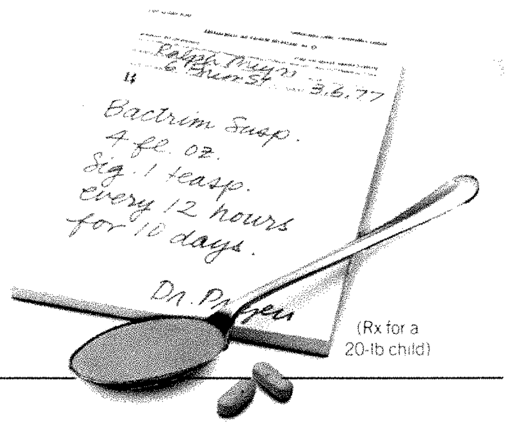
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Bactrim Susp.
4 fl. oz.
Sig. 1 teasp.
every 12 hours
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Dr. P...

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Before prescribing, please consult complete product information, a summary of which follows:

Indications and Usage: For the treatment of urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli, Klebsiella-Enterobacter, Proteus mirabilis, Proteus vulgaris, Proteus morganii.* It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination. *Note:* The increasing frequency of resistant organisms limits the usefulness of all antibacterials, especially in these urinary tract infections.

For acute otitis media in children due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in physician's judgment it offers an advantage over other antimicrobials. Limited clinical information presently available on effectiveness of treatment of otitis media with Bactrim when infection is due to ampicillin-resistant *Haemophilus influenzae.* To date, there are limited data on the safety of repeated use of Bactrim in children under two years of age. Bactrim is not indicated for prophylactic or prolonged administration in otitis media at any age.

Also for the treatment of documented *Pneumocystis carinii* pneumonitis. To date, this drug has been tested only in patients 9 months to 16 years of age who were immunosuppressed by cancer therapy.

Contraindications: Hypersensitivity to trimethoprim or sulfonamides; pregnancy; nursing mothers; infants less than two months of age.

Warnings: BACTRIM SHOULD NOT BE USED TO TREAT STREPTOCOCCAL PHARYNGITIS. Clinical studies show that patients with group A β-hemolytic streptococcal tonsillopharyngitis have higher incidence of bacteriologic failure when treated with Bactrim than do those treated with penicillin. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides. Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended; therapy should be discontinued if a significantly reduced count of any formed blood element is noted.

Precautions: Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In patients with glucose-6-phosphate dehydrogenase deficiency, hemolysis, frequently dose-related, may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim. *Blood dyscrasias:* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic reactions:* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal reactions:* Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis. *CNS reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous reactions:* Drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia in patients; cross-sensitivity with these agents may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies.

Dosage: Not recommended for infants less than two months of age.

URINARY TRACT INFECTIONS IN ADULTS AND CHILDREN AND ACUTE OTITIS MEDIA IN CHILDREN:

Adults: Usual adult dosage for urinary tract infections—1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 10-14 days.

Children: Recommended dosage for children with urinary tract infections or acute otitis media—8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, in two divided doses for 10 days. A guide follows:

Children two months of age or older:

Weight		Dose—every 12 hours	
lbs	kgs	Teaspoonfuls	Tablets
20	9	1 teasp. (5 ml)	½ tablet
40	18	2 teasp. (10 ml)	1 tablet
60	27	3 teasp. (15 ml)	1½ tablets
80	36	4 teasp. (20 ml)	2 tablets or 1 DS tablet

For patients with renal impairment:

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Usual standard regimen
15-30	½ the usual regimen
Below 15	Use not recommended

PNEUMOCYSTIS CARINII PNEUMONITIS: Recommended dosage: 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours in equal doses every 6 hours for 14 days. See complete product information for suggested children's dosage table.

Supplied: *Double Strength (DS) tablets,* each containing 160 mg trimethoprim and 800 mg sulfamethoxazole, bottles of 100; Tel-E-Dose® packages of 100; Prescription Paks of 20. *Tablets,* each containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 40, available singly and in trays of 10. *Oral suspension,* containing in each teaspoonful (5 ml) the equivalent of 40 mg trimethoprim and 200 mg sulfamethoxazole, fruit-licorice flavored—bottles of 16 oz (1 pint).

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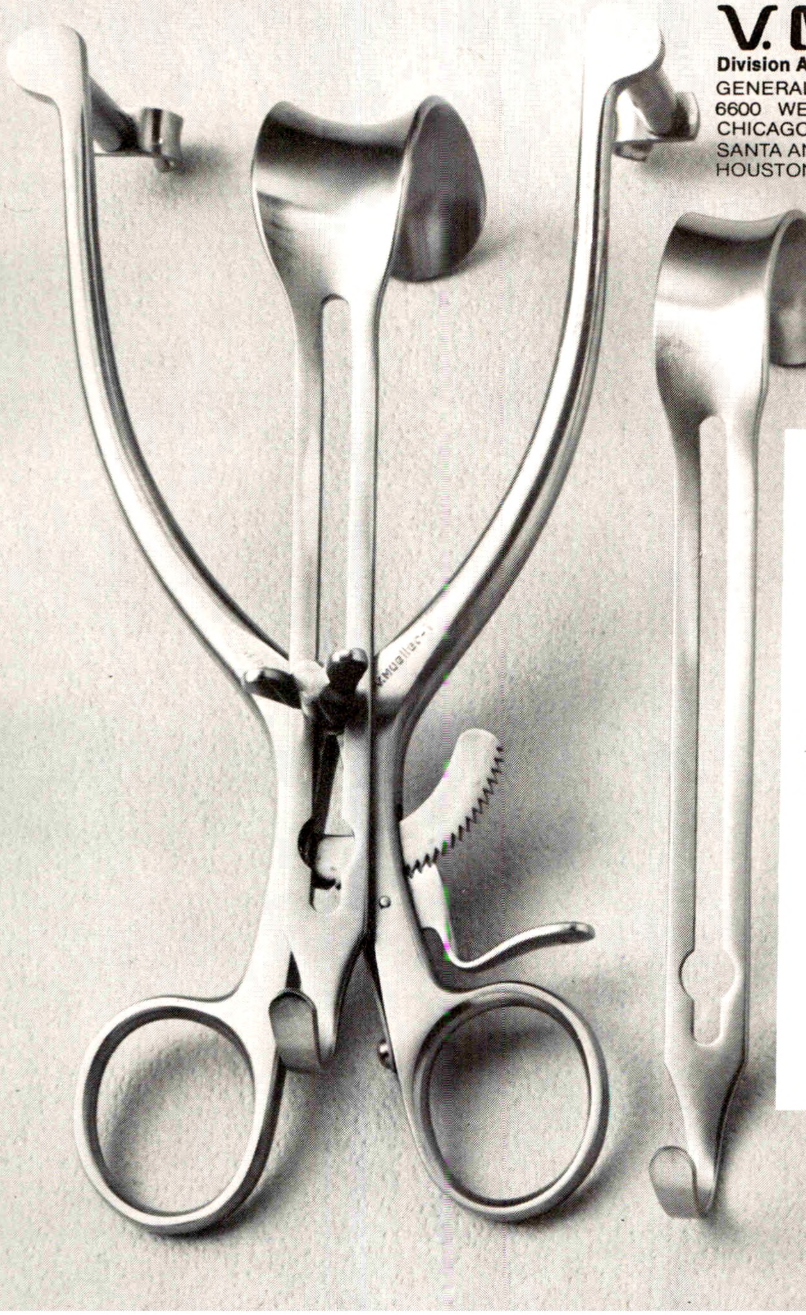

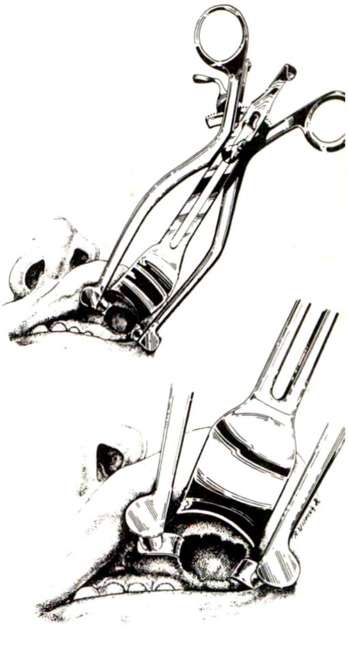

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brand of chlorpheniramine maleate

brand of sustained release capsules

8 mg. 12 mg. capsules, convenient b.i.d. antihistamine

Before prescribing, see complete prescribing information in SK&F literature or PDR. The following is a brief summary.

Indications
Based on a review of this drug by The National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

Probably effective: For the symptomatic treatment of seasonal (hay fever) and perennial allergic rhinitis; vasomotor rhinitis; allergic conjunctivitis due to inhalant allergens and foods; mild, uncomplicated allergic skin manifestations of urticaria and angioedema; dermographism; as therapy for anaphylactic reactions adjunctive to epinephrine and other standard measures after the acute manifestations have been controlled.

Final classification of the less-than-effective indications requires further investigation.

Contraindication: Known hypersensitivity to the drug.

☐ **eases the sneezes***

☐ **dries the eyes***

☐ **nips the itch of allergic rhinitis***

Precautions: Drowsiness is rarely a problem, but caution patients about activities requiring alertness (e.g., operating vehicles or machinery).

Adverse Reactions: Drowsiness, dizziness, dryness of mouth, g.i. upset, and tachycardia. Thrombocytopenia has been reported.

Supplied: 8 and 12 mg. capsules, in bottles of 50; in Single Unit Packages of 100 (intended for institutional use only).

Smith Kline &French Laboratories
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ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY
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IRENE LOEB COHN

1896-1978

IN MEMORIAM

It is always difficult to lose someone who has been a close friend. When one's relationship has been a long-standing one based on deep affection, respect, and a mutual involvement in an absorbing enterprise, the loss, in a very real sense, leaves a void impossible to fill.

Irene Loeb Cohn, Publisher of the *Annals of Otology, Rhinology & Laryngology,* died on February 17, 1978. She leaves us so many memories: a woman of great warmth and intelligence who had a deep devotion to her family; a tremendous pride in the accomplishments of her father, Dr. Hannau Loeb; a wonderful marriage to Julian Cohn. She is survived by two daughters, Mary Grace Cooper and Virginia Cole, six grandchildren and five great-grandchildren.

Irene was born in St. Louis on December 9, 1896. She graduated from Bryn Mawr at a time when most of her friends were not even finishing high school. Her father gave Julian and Irene the *Annals* in 1924 shortly after their marriage because he felt it would be good for Irene to have something to "keep her busy." With the help of her husband she personally handled the myriad details which were essential to publishing a medical journal. She worked intimately with her father, with Lee W. Dean, MD, Arthur W. Proetz, MD, and Ben H. Senturia, MD and Brian F. McCabe, MD, who served as successive medical editors. She always maintained an intense pride and an active involvement in the *Annals*; she was an enthusiastic supporter of any innovation which would improve the publication. She made it abundantly clear that her goal was a journal which maintained the highest professional standards and offered a service to Otolaryngologists. She examined every issue published and never failed to compliment the editorial staff on a job that was well-done. Her long tenure as publisher provides clear evidence of her important contribution to our specialty.

Her children and grandchildren have expressed their desire that the *Annals* remain in the family and be published according to the established family standards. Irene would be very pleased.

Irene was truly a remarkable "lady." It was a privilege to know and to work with her. We will miss her.

BEN H. SENTURIA, MD
BRIAN F. MCCABE, MD

Ann Otol 87:1978

SALIVARY BYPASS TUBE

WILLIAM W. MONTGOMERY, MD

BOSTON, MASSACHUSETTS

SUMMARY — A silicone salivary bypass tube is introduced as an adjuvant to the therapy of the following clinical entities: advanced carcinoma of the pharynx complicated by stricture and/or pharyngocutaneous fistula, traumatic stricture of the cervical esophagus or tracheoesophageal fistula, a stricture of the hypopharynx or cervical esophagus following ingestion of a caustic material, and a stricture of the cervical esophagus following laryngoesophagectomy. The salivary bypass tube is described and illustrated in detail along with the technique for its insertion and removal. Examples of its usage are illustrated by x-rays.

There has long been a need for a device to bypass the pharynx and/or cervical esophagus which have been complicated by a stricture or esophagocutaneous fistula. Such a tube must be well tolerated by the patient and not injurious to soft tissues which are in almost constant motion and have been altered by disease, injury, surgery, or radiation therapy.

In 1955, a polyethylene esophageal tube[1] was introduced as a device to bridge the gap between the pharyngostome and esophagostome following laryngoesophagectomy and first stage reconstruction of the cervical esophagus. In 1962, the esophageal tube was modified in shape and construction (polyvinylchloride).[2] More recently the esophageal tube has further been modified and is now made from silicone (Fig. 1). The esophageal tube has served well for its designed purpose, but it is not of the proper size or shape to be used as a salivary bypass when treating an esophagocutaneous fistula or stricture of the cervical esophagus. Thus, a silicone salivary bypass tube was designed and constructed in three sizes. During the past three years these bypass tubes have been used successfully on 16 patients and have proven to be quite useful for their designed purpose and are now presented for trial by others (Fig. 2).

A postoperative laryngectomy or laryngoesophagectomy esophagocutaneous fistula on occasion will not heal using conservative measures. The constant bathing of tissues which have been altered by surgery, infection, and/or radiation therapy is a prime factor in retarding the progress of healing and fistula closure. A salivary bypass tube (Fig. 3) will direct the saliva into the distal esophagus and allow for spontaneous closure of the fistula or at least permit the tissues to recover sufficiently so as to be a suitable recipient for a more formidable measure such as repair using pedicled skin flap tissue.

A patient with advanced cancer of the pharynx or cervical esophagus often has severe dysphagia and cannot care for his saliva. His disease may be further complicated by a pharyngocutaneous fistula if he has undergone laryngectomy or radiation therapy. A nasogastric feeding tube or gastrostomy is needed for nourishment. The insertion of a salivary bypass tube will serve to control his secretions and allow him to swallow liquids and even semisolids if the large size salivary bypass tube is used (Fig. 4). A feeding tube can be inserted through a very small vertical incision in the salivary bypass tube if the latter is exposed in the cervical region.

External trauma to the larynx and cervical trachea can also include injury to the cervical esophagus as it is com-

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From the Department of Otolaryngology, Harvard Medical School, and the Massachusetts Eye and Ear Infirmary, Boston, Massachusetts.

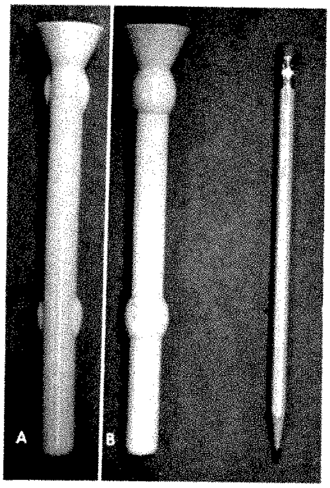

Fig. 1. The silicone esophageal tube used to bridge the gap between the pharyngostome and esophagostome following laryngoesophagectomy. A - Posterior view; B - Anterior view.

pressed between the posterior cricoid lamina and the vertebral bodies. The injury to the cervical esophagus usually occurs at the level of the superior or inferior margins of the posterior cricoid lamina. A stricture of the esophagus can complicate this injury and a tracheoesophageal fistula occasionally occurs at the level of the lower margin of the posterior cricoid lamina. This latter complication is frequently associated with a cricotracheal separation. A salivary bypass tube can serve to prevent or treat a stricture of the cervical esophagus and to stent a tracheoesophageal fistula repair.

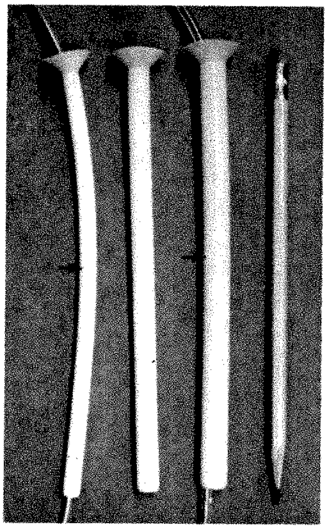

Fig. 2. The three sizes of salivary bypass tubes compared to a pencil. A feeding tube has been inserted through the 8 and 12 mm tubes. The arrows point to the region where a suture may be placed so as to attach the feeding tube to the salivary bypass tube. A 16 mm bypass tube will soon be added to the series.

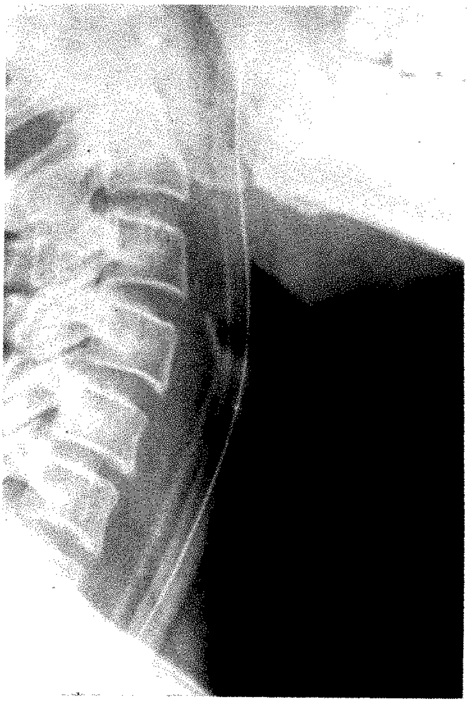

Fig. 3. A salivary bypass tube has been inserted in a patient who has undergone laryngoesophagectomy and reconstruction of the cervical esophagus. A small fistula developed just above the tracheostome on the tenth postoperative day. The leakage ceased promptly and the fistula closed in four days. The salivary bypass tube was removed one week later.

A stricture of the hypopharynx and/or cervical esophagus is a common complication following the ingestion of a caustic material. The insertion of a salivary bypass tube can serve to prevent such a stricture if it is inserted at a reasonable length of time following the burn (Fig. 5). The salivary bypass tube can also be inserted to stent the repair of a chronic stricture of the hypophar-

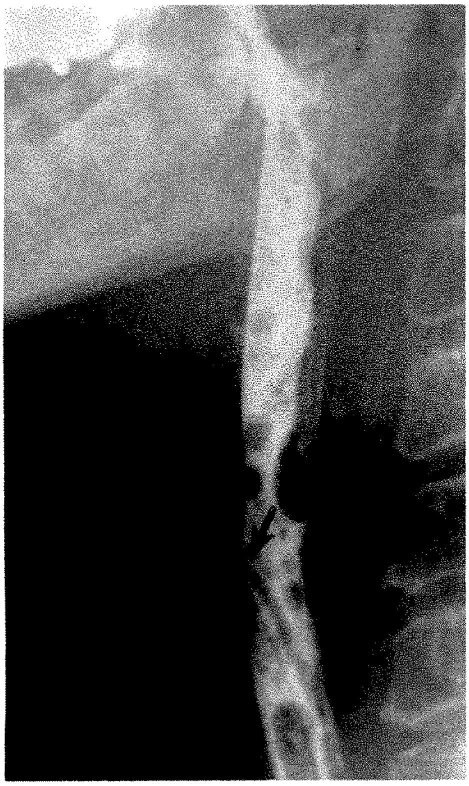

Fig. 4. A barium swallow x-ray showing the salivary bypass tube in place in a patient with advanced carcinoma of the pharynx and a large pharyngocutaneous fistula. In this instance, the feeding tube (arrow) is inserted directly into the bypass tube by way of the fistula at the cervical level.

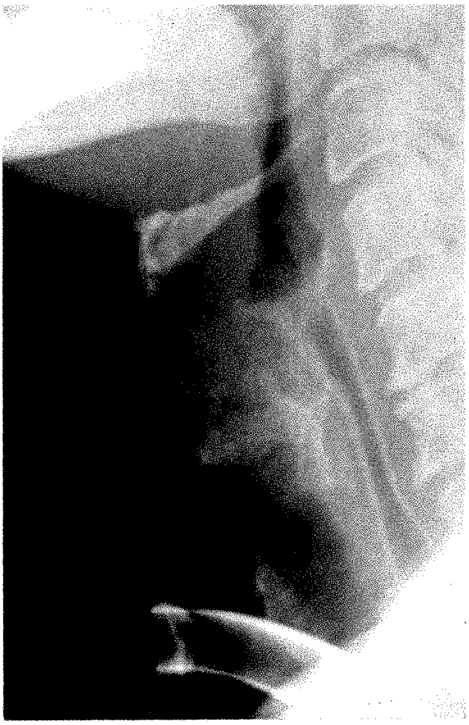

Fig. 5. This x-ray shows the salivary bypass tube inserted into a strictured cervical esophagus of a patient who has swallowed lye. His larynx was rendered functionless and thus surgically closed to prevent aspiration.

ynx or cervical esophagus which has resulted from ingestion of a caustic material.

A stricture of the cervical esophagus following a laryngectomy or laryngoesophagectomy is a very troublesome complication which requires repeated bougienage or an attempt at surgical repair. The salivary bypass tube has been used to stent such a stricture following laryngoesophagectomy. The stricture is dilated with bougies before insertion of the salivary bypass tube (Fig. 6). The bypass tube should remain in place for approximately three weeks when treating this type of stricture.

The silicone salivary bypass tube* is available at the present time in three sizes: 8, 10 and 12 mm (outside diameter). The sizes of nasogastric feeding tubes to be used with each salivary bypass tube are shown in Table 1.

The salivary bypass tube is best inserted using general anesthetic and with direct vision using a Jackson laryngoscope or a battery-powered Foregger laryngoscope such as used by the anesthesiologist. The tube can be inserted by folding up the distal end and grasp-

TABLE 1. SIZES OF SALIVARY BYPASS AND NASOGASTRIC FEEDING TUBES

Bypass Tube (Outside Diameter mm)	*Feeding Tube No.*
8	10
10	12
12	14

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*E. Benson Hood Laboratories, Inc., Duxbury, MA.

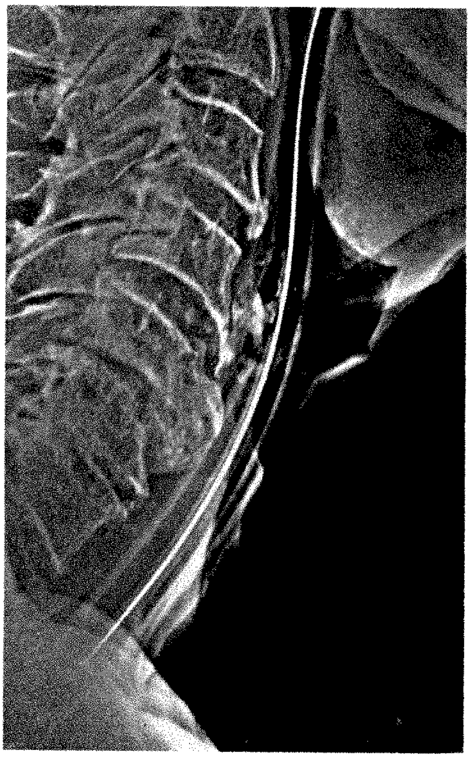

Fig. 6. A benign stricture of the cervical esophagus became apparent eight years following a laryngoesophagectomy. In this case bougienage was used every two months for three years. Following endoscopic bougienage, a 12 mm salivary bypass tube was inserted along with a nasogastric feeding tube. After two days, the feeding tube was removed and the patient nourished himself through the tube while it was in place for three weeks and thereafter required no further bougienage following its removal.

ing this with endoscopic forceps. If there is difficulty with insertion of the bypass tube, McGill forceps and an endotracheal tube stylet are of value. The index finger can be used to push the funnel portion of the salivary bypass tube into position.

It is imperative that the largest size possible bypass tube be used so that the tube will not pass into the stomach. If the surgeon is concerned about this possibility or if nasogastric feedings are to be used, then a feeding tube is inserted along with the salivary bypass tube. To accomplish this, an estimate of the length between the upper cervical region and the stomach is made and a mark placed on the nasogastric feeding tube. The feeding tube is then passed into the nasal cavity and out the mouth. The feeding tube is inserted through the bypass tube to the measured length (mark on the feeding tube) and then fixed to the bypass tube with a nonabsorbable suture. This suture is passed through the wall of the bypass tube and around the feeding tube. The feeding tube and bypass tube are inserted into the esophagus by way of the pharynx as described above.

The salivary bypass tube can be removed with or without anesthesia depending upon whether or not an esophagoscopy is to be carried out at the same time. When removing a salivary bypass tube which has been used along with a feeding tube, the feeding tube is pulled from the nose until the upper end of the bypass tube can be visualized in the pharynx. The bypass tube and distal portion of the feeding tube are removed by way of the oral cavity. The feeding tube is cut with scissors just above the funnel of the bypass tube and the proximal end of the feeding tube removed from the nasal cavity.

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2. Montgomery WW: Reconstruction of the cervical esophagus. Arch Otolaryngol 77: 600-620, 1963

REPRINTS — William W. Montgomery, MD, Dept. of Otolaryngology, Massachusetts Eye and Ear Infirmary, Boston, MA 02114.

Ann Otol 87:1978

EUSTACHIAN TUBE FUNCTION ASSESSED WITH TYMPANOMETRY

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Arthur Loewy, MD
Rosemary A. Corrigan, BSN
Stan B. Osenar, BS
Chicago, Illinois

SUMMARY — On 15 normal ears and 14 pathological ears of adults with intact tympanic membranes, Eustachian tube function was measured by using tympanometry in an effort to reproduce the results published by Holmquist. His method appeared to be a promising tool for clinical determination of Eustachian tube function. However, our results on normal ears were not significantly different from our results on pathological ears and were inconsistent with Holmquist's results. In contrast to Holmquist, 60% of our normal ears were unable to attain achieved negative middle ear pressures of −100 mm to −250 mm H_2O. Our normal ears, as well as our pathological ears, required repeated swallows to normalize negative pressure. Tests in both our groups were not always repeatable even though recorded applied nasopharyngeal pressure was identical. Therefore, our findings do not substantiate this procedure as a useful, reliable clinical tool for measuring Eustachian tube function on ears with intact tympanic membranes.

A functioning Eustachian tube is an integral part of middle ear physiology. Successful surgical repair of middle ears by tympanoplasty also depends upon a normally functioning Eustachian tube. Determination of normal function clearly has a clinical application, and many different tests of tubal function have been employed. These were reported by Ingelstedt and Ortegren,[1] Siedentop,[2] Thomsen[3] and Zoellner.[4] Prior to 1963, almost all were qualitative measurements indicating whether the tube could be made to open. Some of these, namely the Politzer, Valsalva and Toynbee maneuvers, inflate the Eustachian tube and middle ear.

Zoellner[5] pioneered in devising the *tubenwiderstandsmessung* (air pressure resistance level measure), both qualitative and quantitative, which measures the tubal opening pressure by introducing an airstream of constant pressure through the nose into the closed nasopharynx. In his test, the Eustachian tube opening pressure is determined either by noting the noise of escaping air through the eardrum perforation or by observation of outward movement of the eardrum viewed under magnification. It is then recorded as *tubenwiderstand* (TW, air pressure resistance level) in millimeters of water.

Zoellner's method, as well as those of others before him, is not based on the full concept of physiological tube function since there is also a need to reduce negative pressure in the middle ear during swallowing rather than merely permitting inflation. However, recently a method generally known as the middle ear aspiration technique[1] has been developed. It is useful only in patients with a perforated eardrum and is considered the best and most physiological test for this set of circumstances. Using this middle ear aspiration test, one can demonstrate whether the Eustachian tube is capable of releasing physiological pressures applied in the middle ear cavity.

The intratympanic pressure of a normal human ear ranges between +50 to −50 mm H_2O. Occasionally pressures as extreme as +100 to −100 mm H_2O have been encountered, and the physiological testing ranges for middle ear pressure lie between +500 mm H_2O and −250 H_2O.

To perform the Valsalva test, pressures above +700 mm H_2O are required, and in most people more than

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From the Department of Otolaryngology, Abraham Lincoln School of Medicine, College of Medicine of the University of Illinois and the University of Illinois Hospital and Eye and Ear Infirmary, Chicago, Illinois.

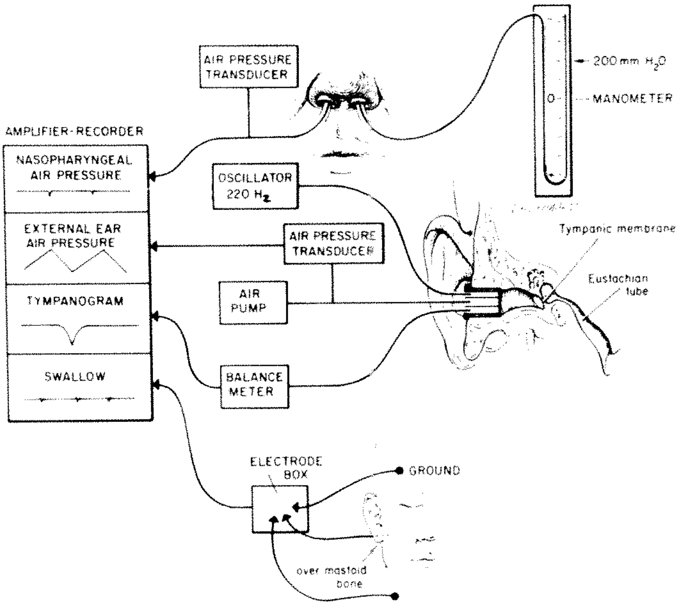

Fig. 1. Diagram of the equipment.

+1000 mm H_2O should be available. In carrying out the Politzer maneuver, positive pressures of 1100 mm H_2O and more are necessary.[2] The Toynbee maneuver, as well as the inflation by Eustachian tube catheter, requires similarly high positive pressures.

The Valsalva, Politzer and Toynbee maneuvers, as well as inflation by Eustachian tube catheter, are tests done in ranges not encountered under conditions of health and, therefore, are not suitable for accurate measurement of Eustachian tube function for the clinician.

How would one assess the Eustachian tube function in prospective divers, aviators and astronauts while selecting them for their professions? Such extremes of physiologic function call for persons who have been carefully chosen because of their physical health. This includes the specification that they have functioning Eustachian tubes. Pressure chamber tests[3] were the only available method to assess Eustachian tube function in these people, but such tests are not useful for routine preemployment or preoperative examinations in the otolaryngologist's office or a clinic setting.

Holmquist[6] described a new test which would function in the presence of an intact eardrum using tympanometry. He presented his method as one useful for office and clinic. It would provide reliable quantitative and qualitative information on the ability of the Eustachian tube to equalize negative middle ear pressure. This seemed to be a promising method for determining Eustachian tube function. Therefore, we planned to reproduce his results in order to determine if this test did indeed provide a means of reliably measuring the function of the Eustachian tube in ears with intact tympanic membranes and also to determine if this technique was practical in the outpatient clinic or physician's office.

METHODS AND MATERIALS

It was our plan to repeat the determinations of middle ear pressure as measured by tympanometry and to assess the reproducibility of Holmquist's "tympanometric method." If valid, this measurement could be the noninvasive equivalent of an aspiration method. Our sample size was determined after a pilot study, definition of acceptable alpha and beta error, and probability that results in the sample would be representative of the population at the 0.95 probability level and at least statistically equal the reliability of Holmquist's report.

Our sample consisted of 15 normal ears and

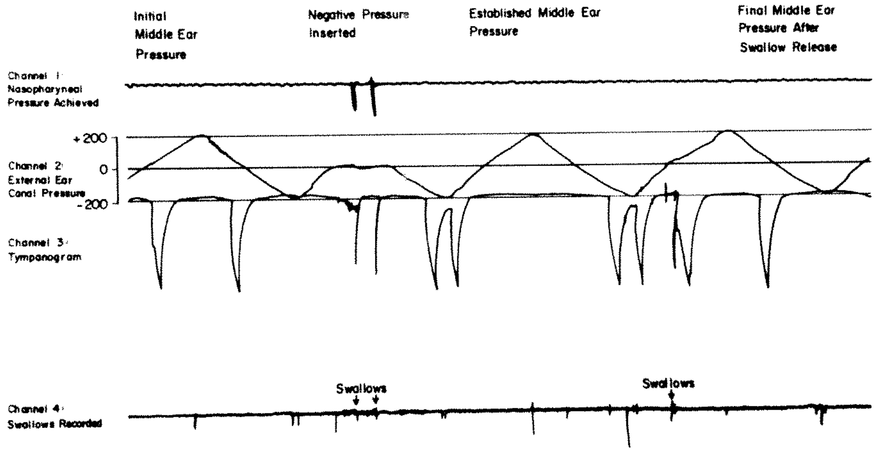

Fig. 2. Sample recording of procedure. Downward peaks on Channel 1 indicate amount of nasopharyngeal pressure achieved during swallowing. Peaks or dips on tympanogram indicate point where pressure in external ear canal and middle ear cavity is equal.

14 pathological ears. Most of the individuals tested were sophisticated adults (otolaryngology residents). Each subject was tested twice. The same ear was used each time and the second test was performed within a few minutes of the first test.

In setting the criteria for selection of normal and pathological ears we followed the same criteria used by Holmquist. Normal ears were those which displayed a normal appearing tympanic membrane as observed under the Zeiss operating microscope. The tympanic cavity was aerated and the tympanic membrane mobile. Hearing thresholds were within the range of 0 to 20 dB (ISO) for frequencies of 500, 1000 and 2000 Hz.

Pathological ears were those which, on the basis of history, had experienced slight problems with Eustachian tube function, intermittently, in the presence of upper respiratory infections or during seasonal allergic problems. We also included those individuals who experienced difficulties while flying, diving, or during other types of rapid descent, e.g., high speed elevator.

The next step was to duplicate the equipment used by Holmquist. We accomplished this in the following manner, as diagramed in Figure 1. In order to create constant negative air pressure in the nose and nasopharynx, our equipment consisted of a motor driven pump, the air pressure output of which was regulated by a manometer. An automatic overflow valve kept the pressure constantly at −200 mm H_2O.

The negative air pressure was transmitted into the nasopharynx of the subject by a tube attached to a rubber nasal tip fitted into one nostril. From the other nostril a second tube led from a nasal tip to an air pressure transducer connected to a Grass polygraph recorder. The nasopharyngeal pressure curve was continuously recorded on Channel 1 of this recorder.

Measurement of the middle ear pressure was accomplished by using an electroacoustic impedance bridge (Madsen Z070). An earplug containing the probe tip of the impedance bridge was inserted into the external ear canal, and the air pump of the impedance bridge was simultaneously connected to an air pressure transducer which transcribed pressure changes in the external ear canal continuously on Channel 2 of the polygraph recorder. The excursions of the tympanic membrane were recorded on Channel 3 of the polygraph recorder by attaching the balance meter of the impedance bridge directly to the recorder. These measurements together represented the variation of the middle ear pressure in relation to the external ear canal pressure.

To obtain a visual recording of when swallows occurred, recording electrodes were positioned respectively on the subject's neck muscle and over the mastoid bone, with a ground electrode positioned on the subject's forehead. An electromyographic recording indicating swallows was transcribed on Channel 4 of the polygraph recorder. A sample recording is shown in Figure 2.

Once the subject was connected to the respective testing apparatus and an air tight seal of the earplug containing the probe tip of the impedance bridge was established in the external ear canal, the initial middle ear pressure was recorded by tympanometry. Following this, the tube attached to the air pressure pump which created a constant pressure of −200 mm H_2O was inserted into the subject's other nostril, pressure was measured and he was asked to swallow. Physiologically, during this swallow the soft palate should close and negative pressure should become established in the nasopharynx. This pressure was then recorded on the polygraph recorder. Simultane-

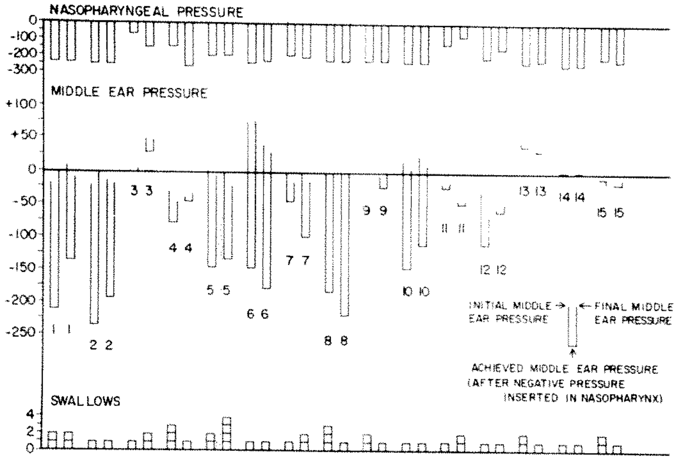

Fig. 3. Testing results on normal ears.

ous to swallowing, Eustachian tube opening should occur, allowing this negative pressure to be transmitted to the middle ear and, at the same time, change the sound pressure level in the external ear canal. A second tympanogram taken at this time recorded the "achieved middle ear pressure."

After the tube providing the flow of negative pressure was removed from the nose and at ambient atmospheric pressure, the subject was again asked to swallow in order to allow the negative pressure to be released from the middle ear via the Eustachian tube and a third tympanogram was recorded. This third tympanogram depicted the "final middle ear pressure."

RESULTS

Our results on normal ears (Fig. 3) showed that of 15 ears tested, 9 (60%) attained an established or achieved negative middle ear pressure level of less than -100 mm H_2O. Of the six who did attain an achieved middle ear pressure level within the -100 to -250 mm H_2O range, four, recording identical applied nasopharyngeal pressure for both the initial test and the repeat test, were unable to attain the same achieved negative middle ear pressure on both tests. Also, two of those ears which did attain an achieved negative middle ear pressure in the -100 to -250 mm H_2O range on either the initial or the repeat test failed to attain this same range again on the corresponding test. Finally, three of our normal ears required more than one or two swallows in order to normalize.

The pathological ears (Fig. 4) show

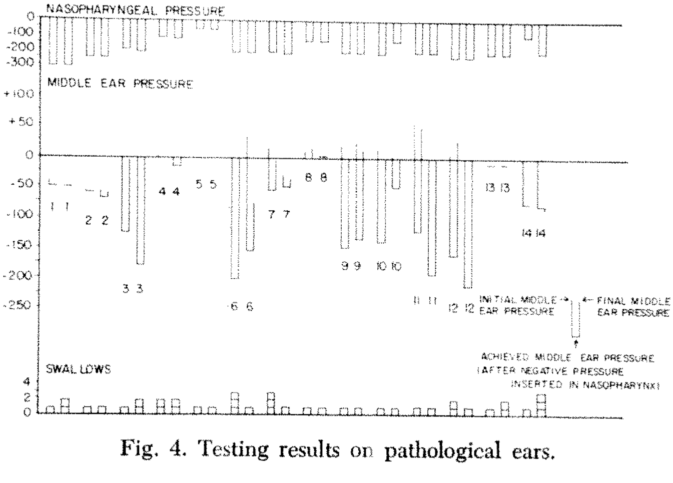

Fig. 4. Testing results on pathological ears.

TABLE 1. COMPARISON OF OUR RESULTS WITH HOLMQUIST'S

N	INITIAL MIDDLE EAR PRESSURE				ACHIEVED MIDDLE EAR PRESSURE				FINAL MIDDLE EAR PRESSURE					
	TEST 1		TEST 2		TEST 1		TEST 2		TEST 1		TEST 2			
	$\bar{x}$	σ	$\bar{x}$	σ	$\bar{x}$	σ	$\bar{x}$	σ	$\bar{x}$	σ	$\bar{x}$	σ		
15	0.91	28.13	-0.83	30.44	-86.9	88.63	-79.8	80.76	-2.66	32.71	-6.31	27.47	SIEDENTOP	NORMAL EARS
20	12.0	17.04	3.00	9.23	-172.5	43.39	-173.6	42.95	3.00	7.33	7.60	14.46	HOLMQUIST	
14	2.76	26.68	-4.91	24.54	-81.1	67.27	-87.5	76.11	-9.11	34.96	-21.1	32.81	SIEDENTOP	PATHOLOGICAL EARS
11	1.82	13.28	0.00	14.83	-135.4	39.06	-126.4	30.09	-54.5	56.56	-54.5	46.98	HOLMQUIST	

that of 14 tested, 7 (50%) had attained an achieved negative middle ear pressure of less than −90 to −200 mm H_2O. One of those attaining the achieved negative middle ear pressure range of −90 to −200 mm H_2O was unable to repeat this on the second test. In ears where the same magnitude of nasopharyngeal pressure was obtained on the first test and the repeat test, the achieved negative middle ear pressure was not always repeatable on corresponding tests. Furthermore, in the majority of cases, pressure equalization was obtained after only one or two swallows.

DISCUSSION

Holmquist reported that all of the normal ears in his study had attained an established negative middle ear pressure level of −100 to −250 mm H_2O which could then be normalized with one or two swallows. He further stated that on repeat testing it was possible to achieve the same range of established negative middle ear pressure.

On the pathological ears, Holmquist reported that all established negative middle ear pressures were in the range of −90 to −200 mm H_2O and to equalize the pressure repeated swallows (more than one or two) were necessary. Furthermore, equalization was not obtainable on all ears when repeated swallows were performed. He also stated that in this group too the established negative middle ear pressure and the pressure after equalization by swallows were reproducible.

Comparing the raw data obtained on our set of pathological ears with Holmquist's reported pathological ears, the results could be considered similar in that they could be indicative of a pathologic condition. However, the results we obtained on pathological ears were not significantly different from the results we recorded on normal ears. In our study, both normal and pathological ears manifested achieved negative middle ear pressures below the −90 to −200 mm H_2O range that Holmquist cites for the pathological ear. Added to this, there were both normal and pathological ears which required repeated swallows (more than two) to obtain equalization. Our normal ear results then were directly contrary to Holmquist's in which all of his reported normal ears achieved a negative middle ear pressure of not less than −100 mm H_2O and all ears were able to equalize with not more than two swallows.

Statistically, we have summarized the results attained on our 15 normal and 14 pathological ears using the following three values: 1) the initial middle ear pressure, 2) the achieved middle ear pressure, and 3) the final middle ear pressure. The values, as shown in Table 1, are expressed as mean values ($\bar{x}$) and their standard deviations (σ) for the first test (T1) and for the second test (T2). The normal cases are depicted in the upper portion of the table and the pathological ones in the lower portion. Both the results of our study and those obtained by Holmquist are included in this table. A difference exists in that Holmquist's were obtained by interpolation from the graphic data in his publication.

In our group of normal ears we found the mean values ($\bar{x}$) for the three measured middle ear pressures in Test 1 (T1) reproducible in Test 2 (T2). Holmquist's results follow the same trend. However, the mean value of Holmquist's achieved middle ear pressures is -173 mm H_2O, while ours is -85 mm H_2O.

Compared to Holmquist's data, our standard deviation (σ) for achieved middle ear pressure measurements is significantly greater. This observation is explained as follows: some of the subjects in our test population are able to perform the test maneuver adequately, while the majority of them cannot. The measurements are scattered over a broad range and this is indicated by the proportionately higher standard deviation values, with a greater variance.

These findings mean that either our test maneuver has to be radically different from that reported by Holmquist, or that by chance the small number of subjects with normal ears measured in both populations divided themselves in such a way that Holmquist tested subjects all of whom could perform the test maneuver, whereas all of ours could not. Comparing the test results in our group of pathological ears with those in our group of normal ears, no significant difference can be found. This suggests that Eustachian tube function in the normal group cannot be differentiated from Eustachian tube function in the pathological group.

Holmquist's group of normal ears differs statistically from his pathological group in only one fact: namely, that in his normal group the mean value ($\bar{x} = -173$) for achieved middle ear pressure is greater than the one for the pathological group ($\bar{x} = -131$).

Our findings do not substantiate this test as a useful tool for qualitative and quantitative measurement of Eustachian tube function in subjects with intact tympanic membranes. It is our feeling that an appropriate tool for assessment of Eustachian tube function in the presence of an intact tympanic membrane has yet to be developed and further investigative effort will be necessary.

CONCLUSIONS

The method of testing Eustachian tube function by using tympanometry, as described by Holmquist, appeared to be a useful clinical method of determining Eustachian tube function in the presence of an intact tympanic membrane. We attempted to duplicate both the procedure and the criteria for subject selection but our results varied from those reported by Holmquist.

Our 15 normal and 14 pathological ears showed a broad range of results occurring in both groups. The test results were not consistently repeatable on the same ear; difficulty in establishing pressure in the nasopharynx was encountered by a number of subjects in both groups; and there was an equal number of normal ears and pathological ears requiring more than two swallows for equalization. Also, a significantly greater standard deviation and lower mean value of achieved middle ear pressure was observed in our normal population, indicating that the majority of our test population was unable to complete the test maneuver. Here they differ significantly with those reported by Holmquist.

In view of these results indicating that our normal group could not be differentiated from our pathological group, we cannot concur with Holmquist that this procedure is a useful and reliable clinical tool for measurement of Eustachian tube function in the presence of an intact tympanic membrane. Further investigation will be necessary to develop an appropriate testing method.

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NINCDS NOTES[*]

1978 BUDGET TOTALS $177 MILLION

The Institute's 1978 budget totals $177 million, an increase of $22 million over last year's funding level. Allocations include: $117 million for grants, a $16 million increase from the '77 budget; $13.0 million for contracts, a $1 million increase from last year; and $7.3 million for training.

Technically, the Institute's budget is based on a continuing resolution, which is a Congressional interim mechanism for continuing funding at the prior year's level until a new budget is passed. This year, use of the continuing resolution resulted from a Congressional deadlock over the abortion issue which stymied passage of the DHEW budget. However, unlike the usual process, this continuing resolution will extend throughout the entire 1978 budget period at the $177 million level agreed to by the conferees.

PROPOSED FY 79 BUDGET

The Administration's proposed 1979 budget for NINCDS totals $181 million. This is $4 million increase over the '78 budget. The Institute plans to spend $12.6 million on contracts, $118.2 million on grants, and $7.3 million on training. The remainder will be spent for intramural research and Institute management.

Hearings by the House Appropriations Committee's Labor HEW-Subcommittee, chaired by Congressman Daniel Flood (D-Pennsylvania), are tentatively scheduled to begin the first week in March. Senate hearings are being conducted by the Senate Appropriations Committee's Labor-HEW Subcommittee chaired by Senator Warren Magnuson (D-Washington).

CLINICIANS ENCOURAGED TO PARTICIPATE IN NEUROSCIENCE MEETING

The annual meeting of the Society of Neuroscience will be held November 5-9, 1978 in St. Louis, MO. Program chairman is NINCDS scientist Jeffery L. Barker, MD. According to the Society, only one percent of the 5,000 members are neurologists; therefore Dr. Barker stresses that clinical contributions to the meeting not only are invited but encouraged. In addition, the program committee feels that the Society's meeting offers an excellent opportunity for clinicians to be brought up to date on basic research directly related to clinical neurology. The meeting will include 14 symposia, 12 workshops and two named lectures, as well as volunteer papers and posters. Information regarding membership and the meeting may be obtained from Dr. Barker, Laboratory of Neurophysiology, NINCDS, NIH, Bldg. 36, Room 2C-02, Bethesda, Maryland 20014 (Tel: 301-496-2414).

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[*] This column is prepared monthly by the Office of Scientific and Health Reports, National Institute of Neurological and Communicative Disorders and Stroke. For further information, write or call Carolyn Holstein, NINCDS/OSHR, NIH Bldg. 31, Room 8A-16, Bethesda, MD 20014. (301) 496-5751.

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BLOOD VESSELS ON REISSNER'S MEMBRANE

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SUMMARY — The purpose of this paper is to investigate in detail the prevalence, localization, and course of the vessels in Reissner's membrane in the well-developed cochleae of individuals of various ages. 1) Of 181 prenatal and postnatal temporal bone specimens, 36 bones (19.9%) showed a total of 43 blood vessels along the surfaces of Reissner's membrane on the scala vestibuli side. In relation to age, 15 vessels were found in 12 out of 16 bones (75%) in the 15-week-old fetus group; 19 vessels were present in 15 out of 58 bones (25.8%) in the 0-1 year age group; 8 vessels were seen in 8 out of 55 bones (14.2%) in the 1-10 year age group; and only 1 vessel was found in 1 out of 52 bones (1.9%) in the 10-102 year age group. 2) Of the 43 vessels, 41 were present in the apical turn, and the remaining 2 vessels were located in the the upper half of the middle turn. 3) There were two types of courses followed by the vessels on Reissner's membrane. Among the 43 vessels observed, 3 vessels ran over the surface of the membrane all the way from the area near the spiral limbus to the vestibular crest. The remaining 40 vessels ran across the fluid space of the scala vestibuli, attached to the membrane somewhere between the spiral limbus and the vestibular crest, and then took their courses along the membrane up to the area of the vestibular crest. 4) The cause of death of the 22 postnatal individuals with vessels on Reissner's membrane was studied. Fifteen individuals expired from congenital anomalies of the heart, brain, digestive organ, lung, or kidney. Among these, congenital heart anomaly cases occurred with an extremely high rate (66.6%). 5) The vessels on Reissner's membrane appeared to occur as an element in the incomplete development of the cochlea. They seemed to be in the process of devascularization, mostly in the first decade, in both the congenital anomaly cases and the noncongenital cases.

Reissner's membrane in man has been said to be an avascular structure.[1-5] Johnsson[6,7] reported the existence of blood vessels on the membrane. Saito[8] described the general rate of occurrence, location, and course of those vessels. He also suggested that these vessels are vestigial structures rather than pathological changes. The purpose of this paper is to investigate in detail, and to describe the prevalence, localization and course, of the vessels on Reissner's membrane in well-developed cochleae in different ages.

METHODS AND MATERIALS

The materials consisted of 181 human temporal bones. Of these, 16 bones were obtained from eight fetuses aged 15 weeks. A total of 165 bones were from 110 postnatal individuals ranging in age from newborn to 102 years old. The prenatal materials had been stored in 10% formalin and were decalcified, dehydrated, embedded in paraffin, and sectioned horizontally or sagittally at 30μ. These sections were stained with Masson's trichrome or a silver nitrate-gold chloride solution. The postnatal materials were fixed, decalcified, dehydrated, embedded in celloidin, and sectioned horizontally at 20μ. Every tenth section was stained with hematoxylin and eosin (H. & E.) and mounted on a glass slide for light microscopic examination.

RESULTS

Of the 181 prenatal and postnatal temporal bone specimens, in 36 bones (19.9%) a total of 43 blood vessels was found along the surface of Reissner's membrane on the scala vestibuli side.

The prevalence by age of the 43 vessels is given in Table 1. Fifteen vessels were found in 12 of 16 bones (75%) in the 15-week-old fetus group; 19 vessels were present in 15 of 58 bones (25.8%) of the 0-1 year-age group; 8 vessels were seen in 8 of 55 bones (14.2%) in the 1-10 year age group; and only 1 vessel was found in 1 of 52 bones (1.9%) in the 10-102 year age

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From the Departments of Otolaryngology and Pathology, University of Pittsburgh School of Medicine, Eye and Ear Hospital, Pittsburgh, Pennsylvania. This research study was supported by NIH Grants NS1121-02 and NS1378T-01.

TABLE 1. BLOOD VESSELS ON REISSNER'S MEMBRANE IN MAN

Age	*TB*	*TB with BV*	*BV*
15-wk fetus	16	12 (75%)	15
0-1 yr	58	15 (25.8%)	19
1-10 yr	55	8 (14.2%)	8
10-102 yr	52	1 (1.9%)	1
Total	181	36 (19.9%)	43

TB - Temporal bones; BV - Blood vessels.

group. The vessels found in the 15-week-old fetuses were still surrounded by a small number of mesenchymal tissue cells (Fig. 1), but in the postnatal cases the vessels were entirely free from mesenchymal tissue cells and were surrounded only by the capillary epithelium (Fig. 2).

In regard to the frequency of appearance of the vessel on Reissner's membrane, one vessel was present in each of 30 bones, whereas two vessels were seen in each of five bones and three vessels in one bone. The bones with the two vessels were of three 15-week-old fetuses and two congenital heart anomaly cases, and the bone with three vessels was of an esophageal atresia case.

The location of the vessels on Reissner's membrane in the various cochlear turns is shown in Figure 3. Of the 43 vessels observed, 41 were present in the apical turn, and the remaining 2 vessels were in the upper half of the middle turn of the cochlea. The vessels varied widely in their locations in the apical turns of the 15-week-old fetuses, but those in the postnatal cases were present chiefly near the apex of the apical turn.

There were two types of courses followed by the vessels on Reissner's

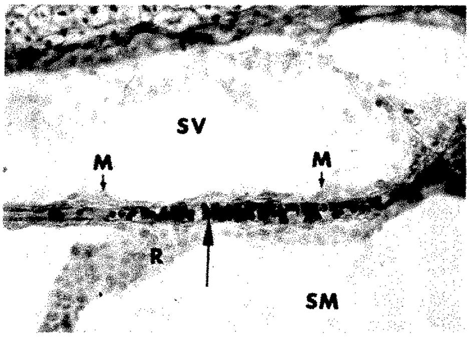


Fig. 1. Blood vessel (arrow) on Reissner's membrane (R) in a 15-week fetus. Note that it is surrounded by a small number of mesenchymal tissue cells (M). SV - Scala vestibuli; SM - Scala media. (Masson's trichrome stain, X 420).

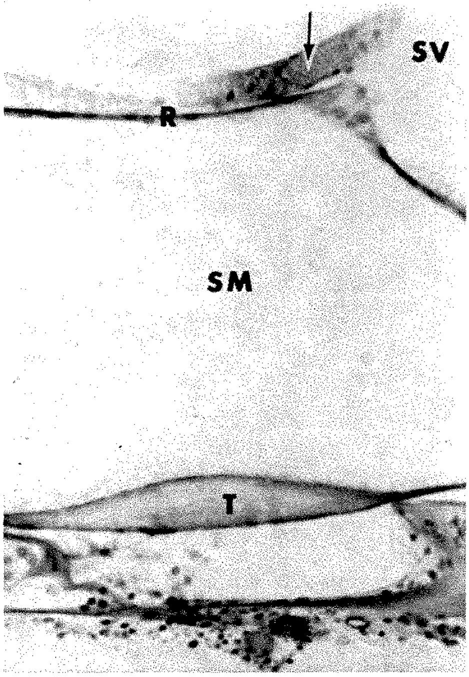


Fig. 2. A 2-day-old infant. The vessel (arrow) is crossed over the scala vestibuli (SV), and is attached to Reissner's membrane (R). The vessel is not surrounded by any mesenchymal tissue cells, but only by the capillary epithelium. SM - Scala media; T - Tectorial membrane. (H & E, X 450).

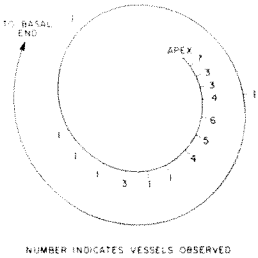


Fig. 3. Schema of area of Reissner's membrane where the blood vessels were observed.

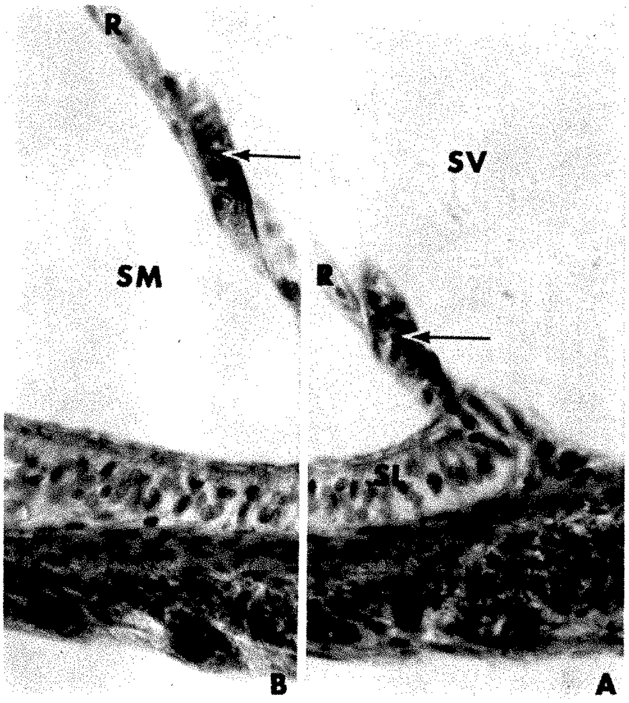
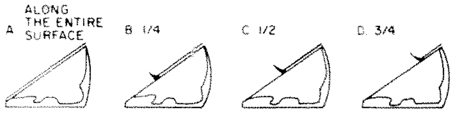


Fig. 4. 8-year-old child. A) The blood vessel (arrow) demonstrates its course near the spiral limbus (SL). B) The vessel (arrow) shows its continuous course along Reissner's membrane (R) to the spiral crest. SV - Scala vestibuli; SM - Scala media. (H & E, 570)

membrane in these temporal bones. In one course, the vessel ran entirely along the membrane from the area near the spiral limbus (Fig. 4) to the spiral crest area where the membrane attaches to the superior portion of the spiral ligament. In the other course, the vessel ran across the scala vestibuli to attach to Reissner's membrane (Fig. 2) in different areas. From those areas, the vessels took their courses along the membrane up to the vestibular crest.

Figure 5 demonstrates the location and number of blood vessels that attach to the surface of the scala vestibuli side of Reissner's membrane. Among the 43 vessels observed, 3 ran across the surface of Reissner's membrane all the way from the area near the spiral limbus to the vestibular crest.



	3 B.V.*	11 B.V.	14 B.V.	15 B.V.
15 WEEK FETUS	0	3	7	5
0-1 YEAR GROUP	1	5	6	7
1-10 YEAR GROUP	2	3	1	2
10-102 YEAR GROUP	0	0	0	1

* B.V.=BLOOD VESSELS

Fig. 5. Schematic drawing demonstrating the location and the number of blood vessels that attach to the surface of the scala vestibuli side of Reissner's membrane.

TABLE 2. CAUSES OF DEATH OF POSTNATAL INDIVIDUALS WITH VESSELS ON REISSNER'S MEMBRANE

Cause of Death	*No. of Cases*	*No. of Cases in Age Group*
Congenital heart anomaly	8 (12)	0-1 : 6 (8) 1-10 : 2 (3) 10-102 : 0 (1)
Brain malformation	2 (9)	0-1 : 0 (4) 1-10 : 2 (5)
Anomaly of the digestive organ	3 (6)	0-1 : 2 (5) 1-10 : 1 (1)
Congenital pulmonary anomaly	1 (3)	0-1 : 1 (3)
Congenital renal disease	1 (2)	0-1 : 1 (1) 1-10 : 0 (1)
Other congenital anomalies: chromosomal, bony, dermal	0 (7)	0-1 : 0 (4) 1-10 : 0 (3)
Infection	3 (11)	0-1 : 2 (5) 1-10 : 1 (6)
Blood diseases	2 (16)	0-1 : 1 (1) 1-10 : 1 (9) 10-102 : 0 (6)
Other acquired diseases: heart, brain, pulmonary, kidney, collagen disease, cancer, others	2 (44)	0-1 : 0 (4) 1-10 : 1 (12) 10-102 : 1 (28)
Total	22 (110)	22 (110)

() - Total number of temporal bones studied in each group.

Of the remaining 40 vessels, 11 were attached to the membrane at a distance approximately one-fourth of the way from the spiral limbus, 14 were attached one-half of the way, and 15 were attached three-fourths of the way from the spiral limbus to the vestibular crest.

The causes of death of the 22 postnatal individuals with vessels on Reissner's membrane are listed in Table 2. Fifteen individuals expired from congenital anomalies of the heart, brain, digestive organ, lung, and kidney. The remaining seven patients died from postnatally acquired diseases.

DISCUSSION

The human Reissner's membrane has been considered to be an avascular structure,[1-5] much as the membrane in the guinea pig,[1,3,5] cat,[3,5] dog,[3,5] or monkey.[3]

A few recent reports have been published describing the blood vessels on Reissner's membrane in the human. Johnsson[6,7] reported a small capillary plexus in two infant cases (1.3%) out of 150 human temporal bones examined. Saito[8] added six more cases (1%), four of which were of children, in an examination of 600 human temporal bone specimens. He also discussed the pathway, location, and rate of occurrence of blood vessels on Reissner's membrane. He suggested that these blood vessels are vestigial structures.

The results obtained in the present study show that out of 181 prenatal and postnatal human temporal bones, 36 bones in 29 cases (19.9%) demonstrated the vessels. The vessels occurred most frequently in 15-week fetuses (75%), less often in newborns (25.8%), and children in the 1-10 year age group (14.2%), and in only one case in the 10-102 year age group (1.9%). Johnsson[7] speculated that a slow devascularization takes place in the inner ear after birth. He stated that all infants have a denser vascularization of the cochlea than adults, and that there is a gradual atrophy of the capillary loops with increasing age, especially during the first decade. These descriptions and our observations of the rate of occurrence with age appear to support the existence of gradual devascularization of Reissner's membrane in the first decade.

In our study, 41 out of the 43 vessels on Reissner's membrane were observed in the apical turn. This finding is similar to that described by Saito.[8] The remaining two vessels, however, were seen in the upper half of the middle turn, and no capillary was seen in the lower half of the middle turn or in the basal turn. Those vessels in the apical turn were seen in a wide range of sites in 15-week fetuses, whereas those in the postnatal cases were apt to appear in the area near the helicotrema. It appears that this tendency is related to the fact that the scala vestibuli begins to develop from the area near the oval window and continues to develop toward the helicotrema area in the apical turn.[9,10]

Of the 43 capillaries in this study, 3 ran obliquely from the area of the spiral limbus to the vestibular crest over Reissner's membrane and took the same course as Nabeya described in the rabbit.[3] The course of the other 40 vessels was the same as that described by Saito,[8] in which the vessels branched off from a radiating arteriole, ran across the scala vestibuli, attached to the membrane, and finally reached the vestibular crest. Watanuki *et al*[5] reported that "the epithelial cells of Reissner's membrane grew to a larger size as they moved from the inner (the area close to the spiral limbus) to the outer side (spiral crest)." If the mesenchymal cell layer of the membrane moved together with the epithelial cells, the location where the blood vessels attach to the membrane would be observed to be closer to the spiral crest with advancing age. The location of the attachment of the vessels in our cases however, was not particularly localized to any part of Reissner's membrane with different ages. Therefore, it appears that the vessels on the membrane are not associated with the movement of the epithelial cells.

Seven of 22 cases were related to acquired diseases and represent 9.9% of all acquired cases (71) examined. This rate is much higher than those previously reported by others (1.3% by Johnsson,[6,7] and 1% by Saito[8]). It is also of interest to note that the rate in congenital anomaly cases (38.5%), particularly in congenital heart anomaly cases (66.6%), is much higher than that in postnatally acquired disease cases (9.9%). In view of these factors, the vessels on Reissner's membrane appear to be seen under conditions involving incomplete development of the cochlea. The vessels seem to be in the process of devascularization, mostly in the first decade, in both the congenital anomaly cases and in the noncongenital cases.

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MELANOCYTE SYSTEM OF THE ENDOLYMPHATIC DUCT AND SAC

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SUMMARY — One hundred fourteen human temporal bones from 64 individuals were studied for the presence of melanized melanocytes about the endolymphatic duct and sac. Specimens were from Caucasians (104), Orientals (6) and Negroes (4). Of the specimens from people above nine years of age 79% demonstrated melanized melanocytes about the endolymphatic duct and sac, as well as occasionally about blood vessels in the adjacent bone. These represented 74% of the Caucasian and 75% of the Negro and Oriental individuals. Pigment granules were noted in occasional epithelial lining cells and in macrophage-type cells within the lumen. Heavily melanized melanocytes were noted in five of six specimens of Ménière's disease (all from Caucasian individuals), five of five specimens with previous labyrinthitis (two of which were from a Negro woman), and in occasional specimens from patients with presbycusis, metastatic carcinoma (three of the four adult Oriental patients), chronic otitis media, otosclerosis and lymphoma, as well as in several apparently normal specimens. No clear cut correlation of degree of melanization with specific disease processes can be discerned.

Melanocytes have been described in the cochlea and vestibular labyrinth[1,2] but have not been recognized as such in the endolymphatic duct and sac. Zechner and Altmann,[3] in a study of 14 human temporal bones, described pigment about the intermediate part of the sac as most probably melanotic, but did not mention melanocytes. In a previous study,[4] the author demonstrated melanocytes in the loose perisac tissue, referring erroneously to them as melanophores.

In the present study, 114 human temporal bones from 64 individuals were studied for pigment in the endolymphatic duct and sac regions. One hundred four specimens were from Caucasian individuals, six were from Orientals and four were from Negroes. The specimens were fixed in 10% neutral buffered formalin, decalcified with the tetrasodium salt of EDTA, embedded in parlodion, and stained with H. and E.

RESULTS

Eighty-three of 105 temporal bones from individuals above nine years of age demonstrated dendritic melanized melanocytes in the periductal and/or perisac tissue. These included two specimens from an adult Negro woman and three of four specimens from adult Oriental individuals. The remaining 100 specimens demonstrating melanized melanocytes were from Caucasian patients.

As well as could be determined, the pigment was always in melanocytes. When only a few were present, the melanocytes were usually adjacent to the bone margin of the vestibular aqueduct of the intermediate endolymphatic sac. They were similar in appearance to those in the vestibule and cochlea, with long, delicate dendritic processes and a central oval nucleus, and varied only in degree of melanization. Lightly melanized melanocytes were more readily seen with the light source decreased in intensity.

When melanocytes were present in larger numbers, they were not only adjacent to the bone of the vestibular aqueduct, but were also in the loose perisac tissue and in the subepithelial region of the isthmus and sac, at times obviously related to capillary walls (Fig. 1A). Pigmented melanocytes were also seen in many specimens about the

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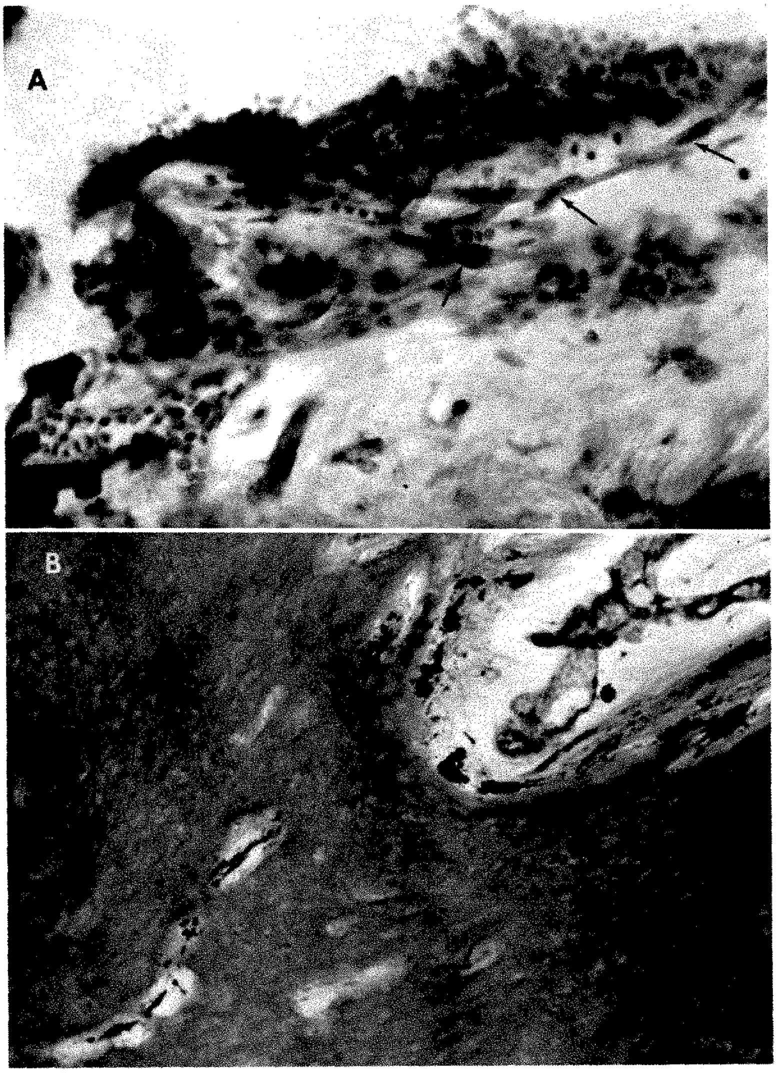

Fig. 1. A) Lightly melanized melanocytes in subepithelial region of intermediate sac and along longitudinally cut capillary. Note dendritic processes attached to each other, and aggregates of pigmented cells, lower left. (H&E, X455) B) Elongated melanocytes along vessels within the bone (left) and melanocytes, swollen with pigment in perisac tissue (right). (H&E, X182)

blood vessels within the bone surrounding the isthmus and sac (Fig. 1B). In a few temporal bones, small foci of pigmented melanocytes were present in the connective tissue between the distal sac and temporal bone surface.

Specimens from individuals below nine years of age were devoid of pigment, except for the temporal bones of a 4-day-old Negro male which demonstrated occasional lightly melanized melanocytes in the perisac region. No melanized melanocytes were seen in two specimens from an 8½-year-old Oriental male. When melanized melanocytes were absent, one could not rule out the presence of amelanotic melanocytes.

Occasionally, and more easily seen with the light source decreased in intensity, small numbers of the lining epithelial cells of the isthmus and/or inter-

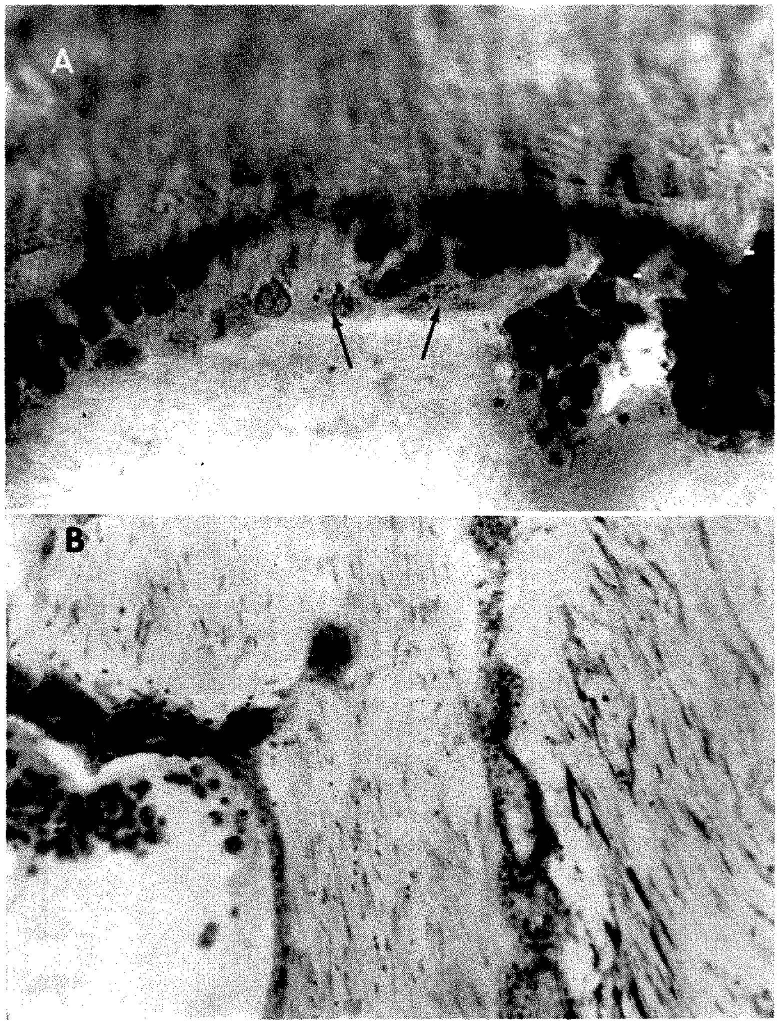

Fig. 2. A) Individual dark granules in cytoplasm of lining epithelial cells (arrows), intermediate portion of sac. (H&E, X728) B) Numerous melanocytes in perisac tissue on right with delicate dendritic processes. In lumen of sac (left) are clusters of macrophage-type cells containing pigment. (H&E, X182)

mediate endolymphatic sac demonstrated individual sharply demarcated gold-brown granules within their cytoplasm, similar to the individual granules seen in the lightly melanized melanocytes (Fig. 2A). Occasional clusters of macrophage-type cells containing gold-brown pigment granules were noted within the lumen of the endolymphatic sac in some specimens (Fig. 2B).

Thirty-three temporal bones from 25 individuals demonstrated foci of densely melanized melanocytes, either unilaterally or bilaterally. In these, the pigment cells were clustered together with dense brown-black aggregates of melanin distending the melanocyte cell body and processes (Fig. 1B). They were often located within the subepithelial regions within "spaces" (Fig. 3). Transverse sections of melanocyte dendritic processes, swollen with pigment, could be identified as such by their smooth contour.

The densely pigmented specimens

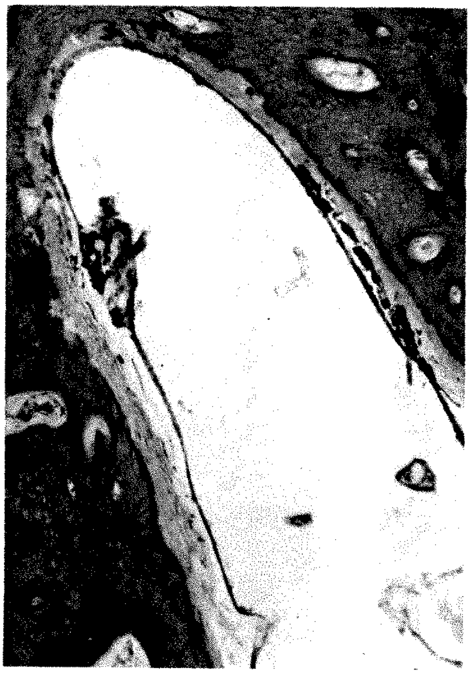

Fig. 3. Heavily melanized melanocytes clustered predominantly in subepithelial "spaces," intermediate portion of endolymphatic sac. (H&E, X455)

were from patients ranging in age from 25 to 75 years and included five of six specimens of Ménière's disease (all Caucasian individuals) and five of five specimens with previous labyrinthitis (two from a Caucasian woman with previous mumps infection, two specimens from a Negro woman with tertiary syphilis and one of unknown etiology from a Caucasian woman). The remaining specimens with prominent melanization were from occasional cases of presbycusis (from Caucasian individuals), metastatic carcinoma (three of which were from Oriental individuals; the fourth Oriental specimen had only a few demonstrable melanized melanocytes and no metastatic carcinoma), chronic otitis media, otosclerosis, lymphoma, and also included several apparently normal temporal bones, all the last groups from Caucasian individuals.

DISCUSSION

Most temporal bones from individuals above nine years of age demonstrated the presence of melanized melanocytes, ranging in number from rare, lightly pigmented melanocytes near the bone of the intermediate vestibular aqueduct, to larger numbers of more heavily melanized melanocytes along vessels in the surrounding bone and in the subepithelial regions of the duct and sac, often related to blood vessels and epithelial lining cells.

Occasional epithelial lining cells of both the duct and sac demonstrated small numbers of individually occurring, sharply demarcated gold-brown granules within their cytoplasm. Clusters of pigment-laden macrophage-type cells were present occasionally within the sac lumen, either representing sloughed off epithelial cells or macrophages present originally in relation to the epithelial cells.

Thirty-three specimens demonstrated prominence of densely pigmented melanocytes. They included five of six specimens of Ménière's disease, all from Caucasian individuals, and all five specimens of previous labyrinthitis, (two of which were from a Negro woman). Several apparently normal specimens also had heavily melanized foci as did occasional specimens from patients with presbycusis, metastatic carcinoma, chronic otitis media, otosclerosis and lymphoma. Other specimens with similar diagnoses did not demonstrate increased melanization of melanocytes. No definite correlation can be made at this time relating increased prominence of heavily melanized melanocytes to a particular disease process, other than perhaps expecting a higher incidence in specimens with Ménière's disease and specimens with previous labyrinthitis.

Recent reports in the literature[5,6] describe individually-occurring enzyme-producing cells in the respiratory and gastrointestinal tracts, which are derived from the neural crest and have amine precursor uptake functions. They are referred to as APUD cells or as the "*a*mine *p*recursor *u*ptake and *d*ecarboxylase activity" system. These cells secrete various hormones and demonstrate specific fluorescence after treatment with L-Dopa, and subsequent decarboxylation into dopamine. The presence of APUD cells within the target tissue itself may serve to effect rapid enzymatic changes.

Melanocytes, also derived from the neural crest, and found so readily within various portions of the inner ear, may also effect rapid changes, either involving blood vessel walls and/or epithelial cell function and/or basement membrane permeability.

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NATIONAL HEARING ASSOCIATION

The National Hearing Association, a newly formed, not-for-profit foundation dedicated to the cause of cure and prevention of deafness, opened its national headquarters offices at 1010 Jorie Boulevard (Suite 308), Oak Brook, IL 60521 on February 3, 1978. Some of the country's leading otologists and interested business and community leaders are emphasizing the fact that funds available to support research for the cure and prevention of deafness are far less than funds devoted to other handicaps that affect a much smaller percentage of the population. The National Hearing Association is dedicated to correcting this deficency in research funding.

Mr. M. A. Self is Chairman, George E. Shambaugh, Jr., MD is President and J. William Wright, Jr., MD is 1st Vice-President of the Association.

Those interested in helping the National Hearing Association by becoming active members and/or assisting in chapter development, fund raising, and other activities are urged to write: National Hearing Association, 1010 Jorie Boulevard (Suite 308), Oak Brook, IL 60521.

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NEOGLOTTIC RECONSTRUCTION AFTER TOTAL LARYNGECTOMY

A PRELIMINARY REPORT

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SUMMARY — This paper is a preliminary report on neoglottic reconstruction of the larynx after total laryngectomy following the techniques described by Staffieri. Also included are general observations on the criteria for selecting candidates for this procedure. At the University of Texas Medical Branch in Galveston, this procedure has been attempted on eight candidates. Reconstruction was accomplished in six, of whom five achieved satisfactory speech, providing an 80% success rate. One of the five did not like the quality of his voice and refused to use it. The sixth produced speech with difficulty and is still undergoing speech therapy. One patient died from recurrence before a second stage could be carried out, and another patient did not have sufficient tissue for neoglottic reconstruction after total laryngectomy. Three patients developed salivary fistulas at the drain site, but all closed spontaneously with the application of pressure. From this data, one may conclude that this technique offers much potential and warrants further study.

This paper is a preliminary report on neoglottic reconstruction of the larynx after total laryngectomy. This technique, developed by Staffieri,[1] has been utilized in more than 200 patients who have achieved successful voice reproduction postoperatively.

At the University of Texas Medical Branch in Galveston, this procedure has been attempted on eight occasions. One patient did not have sufficient tissue remaining after laryngectomy to perform the reconstruction. A second patient, who had preoperative radiotherapy, had only the first stage of the procedure. Before the second phase could be completed, the patient developed skin metastases and died.

Of the six patients in whom the reconstruction was completed, four developed good speech, one developed speech with difficulty, and the last, while able to phonate, did not like the quality of his neoglottic voice and refused to use it.

TECHNIQUE

A standard total wide field laryngectomy, using the modification described by Staffieri,[1] was attempted in all cases. After mobilizing the larynx in the standard manner, a permanent tracheostomy is created by excising a circle of cartilage at the level of the third and fourth tracheal rings. A similar, but slightly larger area of skin is excised over the tracheal stoma, and the skin epithelium is sutured in apposition to the tracheal mucosa. The trachea is transected at the subcricoid level, with care being taken not to enter the postcricoid esophagus. The dissection is then carried cranially, developing a flap of the postcricoid mucosa (Fig. 1). After this dissection, the larynx is entered at the point furthest from the tumor, and a standard resection is carried out. The lower margin of the resection is connected to the previously described inferior dissection at the level of the aryepiglottic folds and arytenoids. At completion of the resection, bleeding is controlled, using standard techniques.

Attention is then directed to the posterior cricoid mucosal flap. At a point in the midline that is approximately at the center of the top of the trachea, 4/0

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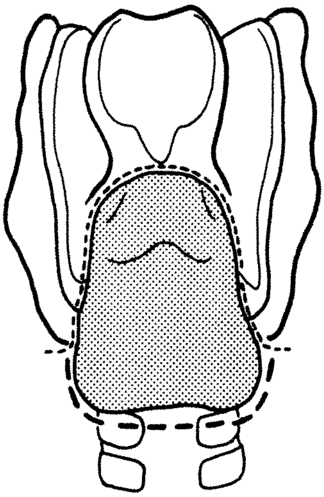

Fig. 1. The shaded area indicates the region from which the postcricoid flap is developed. The heavy dotted line indicates the standard mucosal cuts, and the light dotted line indicates the mucosal cuts used in the neoglottic procedure.

silk holding sutures are placed. A cutting cautery is used to incise through the muscle and submucosa to the pharyngeal mucosa (Fig. 2A). At this point, two more sutures are placed in the mucosa, which is pulled through the incision in the muscle (Fig. 2B). Using a cutting cautery, the mucosa is incised for approximately 8 mm (Fig. 2C). The mucosal edges are then sewn to the submucosal and muscle layers with 4/0 silk. One suture is placed in each corner, as shown (Fig. 2D). The pharyngeal flap is placed over the open top of the trachea and sewn into position in two layers, using absorbable sutures (Fig. 3).

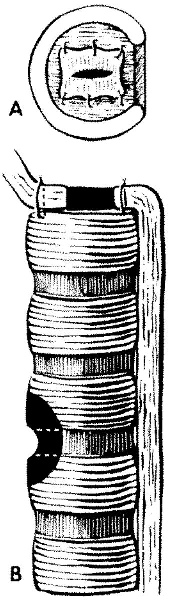

Fig. 3. A) View of neoglottis after it has been sewn in place (viewed from below). B) Side view of neoglottis sewn in position.

The hyoid was left intact in all of our patients. In the original reports, Staffieri[1] describes a horizontal closure with this flap. Although this method

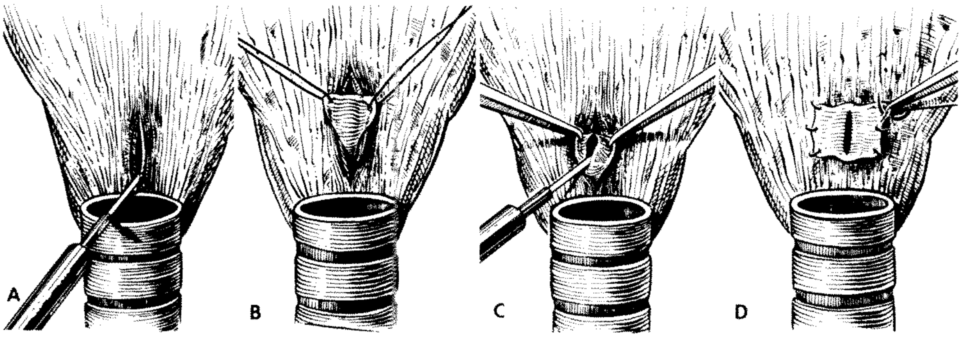

Fig. 2. A) A cutting cautery is used to make an incision through the pharyngeal muscle and submucosa. B) Holding sutures are placed in the pharyngeal mucosa, which is pulled through the opening previously created in the muscle. C) The mucosa is incised for approximately 8 mm with a cutting cautery. D) The pharyngeal mucosa is sewn back with 4/0 silk sutures.

has been attempted on several occasions, it has been abandoned due to the excessive tension produced on the flap. Hemovac® drains are placed in the gutters on each side of the pharynx, and the skin is closed in layers.

SURGICAL INDICATIONS

Neoglottic reconstruction appears to be possible in most lesions requiring a total laryngectomy. However, this procedure is contraindicated in those patients who have postcricoid or postarytenoid involvement and in those patients whose subglottic extension requires a low tracheal resection.

In patients who have had prior radiotherapy, Staffieri[1] recommends the formation of the flap and tracheostoma in the method outlined, with reconstruction delayed until healing is complete. At that time, the neoglottis is created under local anesthesia via the tracheostoma.

To date, all but two of our patients had either T_3 or T_4 endolaryngeal epidermoid carcinomas. In Case 2, the lesion was so extensive that the mucosal flap could not be developed without compromising the resection. In Case 4, the lesion, which involved the pyriform sinus, compromised the formation of the mucosal flap. In this case, a standard resection was performed, and the flap was created by mobilizing the esophagus and performing a slightly lower resection of the trachea. The neoglottis was formed in the mobilized esophageal mucosa.

CASE REPORTS

Case 1. A 56-year-old Negro male presented with a two month history of hoarseness. A squamous cell carcinoma involving the right true and false cords with minimal subglottic extension was found. The vocal cord was fixed, and no nodes were present.

A total laryngectomy with neoglottic reconstruction was performed. Postoperatively the patient healed primarily and was able to phonate on the seventh day. Subsequently, he was discharged; but when seen two weeks postoperatively, he was aspirating on water only. He was instructed to insert a cuffed tracheostomy tube when drinking water and was able to prevent aspiration satisfactorily in this way.

Case 2. A 75-year-old Negro male was transferred from another institution with a tracheostomy tube in place. The tracheostomy had been performed 24 hours previously for airway obstruction. Upon evaluation, the patient was found to have a lesion involving the entire pyriform sinus.

He underwent a total laryngectomy and right radical neck dissection. After excision of the tumor, the remaining tissue was insufficient for neoglottic reconstruction. Therefore, a normal closure was carried out, and postoperative radiotherapy was given.

Case 3. A 64-year-old Caucasian male presented with a seven month history of hoarseness. He was found to have a squamous cell carcinoma of the left true cord, left false cord and aryepiglottic fold. The cord was fixed, and no nodes were present.

He underwent a total laryngectomy with neoglottic reconstruction. Postoperatively he developed a salivary fistula from his Hemovac® drain site, which closed spontaneously with pressure in four days after removal of the drain. Although this patient phonated in 15 days, he had considerable difficulty with aspiration of liquids. The neoglottis was examined from the tracheostomy site, and it was found that the neoglottis had migrated from its original central position to the posterior lip of the tracheostomy remnant. Since the patient had good voice and was able to control aspiration of fluids with a cuffed tracheostomy tube, he declined revision.

Two months later he was still aspirating on all fluids, and it was decided to revise the neoglottis. The length of the neoglottis was reduced by approximately 50% via the tracheostoma. The procedure produced a dramatic reduction in the amount of aspiration, which was easily controlled with a cuffed tracheostomy tube. He maintained an excellent voice. Postoperatively he underwent radiotherapy.

Case 4. A 67-year-old Caucasian male presented with an eight week history of hoarseness. A lesion involving the left vocal process, true cord, the anterior commissure and one third of the opposite cord was found. A subglottic extension of 2-3 mm was noted.

A vertical hemilaryngectomy was attempted. At surgery, the subglottic extension was found to be greater than anticipated, and a complete resection could not be achieved by a partial procedure. Therefore, a total laryngectomy with neoglottic reconstruction was performed without complication.

Postoperatively there was a salivary leak in the left Hemovac® drain. The drain was removed, and the fistula healed spontaneously in four days with the application of pressure. The patient produced good speech with no aspiration 20 days postoperatively and underwent postoperative radiotherapy.

Case 5. A 63-year-old Caucasian male presented with a two week history of painful swelling in the right neck. The patient had a lesion of the aryepiglottic fold, false cord, vallecula and pharyngeal wall that involved only the right side. He also had a 1 cm node in the right jugulodigastric area.

A preoperative course of 4500 rads was given. Six weeks later he underwent a total laryngectomy and right radical neck dissection. A "neoglottic-type" flap was created and sewn in place; but due to prior irradiation, the neoglottic opening was not created at that time. Primary healing occurred, but three weeks postoperatively the patient developed skin metastases and quickly succumbed to his disease. The neoglottic aperture was never created.

Case 6. A 60-year-old Caucasian female, presented with a six month history of a sore throat. A lesion involving the entire right pyriform sinus, including the aryepiglottic fold, was found. A 2 x 2 cm node was present in the right neck.

A standard total laryngectomy was performed. Due to the size of the lesion, it was impossible to make a standard "neoglottic-type" flap. Therefore, a dissection was performed between the trachea and the esophagus, which allowed the esophagus to be mobilized cranially and utilized as the neoglottic flap. The first tracheal ring was also resected to facilitate this maneuver, and the neoglottis was then created in the esophageal flap.

Seven days postoperatively the patient appeared to be healing well, and feeding was begun. At this point, she was able to produce speech. However, on the tenth day, she developed a salivary fistula from one of the Hemovac® drain sites. The nasogastric tube was replaced, the Hemovac® drain was removed, and a pressure dressing was applied. The fistula closed in 72 hours. On the 11th day postoperatively, a course of chemotherapy using bleomycin and methotrexate was begun. On the 21st day postoperatively, another smaller fistula developed in the midline at the site of the incision. Once again, the nasogastric tube was placed, and a pressure dressing was applied. This fistula closed spontaneously in eight days.

Since that time, the patient has produced speech with difficulty. She lives many miles from the center, so she was not able to continue speech therapy. However, she will be returning for postoperative radiotherapy, and speech therapy will be resumed at that time.

Case 7. A 65-year-old Caucasian male presented with a 10 day history of hoarseness, a sore throat and a 12-pound weight loss in the past three months. On direct laryngoscopy, he was found to have a right true vocal cord lesion that extended onto the false cord subglottically for 5 mm. The cord was fixed. The patient underwent a total laryngectomy with neoglottic reconstruction.

The postoperative course was complicated by a small fistula that developed on the eighth day. This was successfully treated by reinstituting nasogastric tube feedings and applying pressure to the neck. The patient was able to phonate but did not like the quality of his voice and refused to use it. No aspiration occurred. He completed postoperative radiotherapy without sequelae.

Case 8. A 64-year-old Negro male presented with a four month history of hoarseness. A lesion of the left false cord and the left true cord with 2-3 mm subglottic extension was found. The cord was fixed.

The patient underwent a total laryngectomy with neoglottic reconstruction. Postoperatively he healed primarily, talked after three weeks and could swallow without aspiration. The patient completed postoperative radiotherapy without complications.

DISCUSSION

An 80% success rate was achieved in those patients who actually received the neoglottic reconstruction. Of the six patients in whom reconstruction was completed, one refused to use his voice, and a second had extreme difficulty with phonation. The latter case can probably be corrected by increasing the size of the neoglottis. Aspiration occurred only in the first two cases. In one of these cases, the neoglottis was found to be on the posterior lip of the trachea. The location of the neoglottis is probably important, since prevention of aspiration may depend partially upon the shielding effect of the base of the tongue. In all cases, a subsequent attempt was made to situate the neoglottis anteriorly to utilize the normal action of the tongue maximally. None of these cases had any aspiration problems. We believe, as does Staffieri,[1] that it is important to maintain the glossal musculature intact by leaving the hyoid in place so that the tongue may act in a coordinated manner during deglutition.

Three patients developed fistulas. In our experience, this is a high rate of fistula formation. Since all but one of the patients were nonirradiated, this complication was unexpected. At present, we are unable to explain this high rate of fistula formation.

All patients, except the patient discussed in Case 5 who died of his disease, have disease-free intervals of three to six months. There have been no recurrences to date.

Using Staffieri's[1] technique, vocal rehabilitation was achieved in 80% of our cases. In the authors' opinion, this technique offers great potential for the following reasons:

1) No compromise is required in the surgical resection. 2) It is a simple procedure. 3) In nonirradiated patients, it is a one-step procedure. 4) No mechanical parts are required. 5) Rehabilitation time is short. 6) Long phonation time produces much greater intelligibility of speech.

It has the following disadvantages: 1) Voice is hoarse. 2) Tracheostomy is necessary. 3) One hand is needed to block the stoma when phonating. 4) Minor aspiration problems may develop.

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OTOLARYNGIC PATHOLOGY TRAINING PROGRAM

A training program on otolaryngic pathology, presented by the Armed Forces Institute of Pathology (AFIP) in conjunction with the Committee on Otolaryngic Pathology, AAOO, is currently being offered at the Department of Otolaryngic Pathology, AFIP. The course covers both temporal bone pathology as well as surgical pathology of the head and neck area.

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EFFECTS OF PUTATIVE TRANSMITTERS ON AFFERENT COCHLEAR TRANSMISSION

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SUMMARY — Putative transmitters and related substances were perfused through the guinea pig scala tympani while monitoring the compound action potential of the cochlear nerve (AP) and the cochlear microphonic potential. Various substances were then ranked according to their ability to reduce the AP. The more active compounds ranked: methysergide (1 mM) > ATP (10 mM) = tyramine (10 mM) > salicylate (10 mM) > bicuculline (10 mM) > aspartate (10 mM) > glutamate (10 mM) > citrate (10 mM) > dextrose (100 mM) > glycine (100 mM) > GABA (100 mM) > prostaglandin E_2 (1 mM) > serotonin (10 mM). The activity of substances at 100 mM indicates a physical, osmotic change in the cochlear structure. Activity at 10 mM and 1 mM indicates afferent transmitter-like activity for the putative transmitters and interference with the endogenous transmitter for related substances. It is concluded that several substances can be eliminated as afferent transmitter candidates, while others warrant further examination.

Mammalian cochlear hair cells are innervated by both afferent and efferent nerve fibers.[1] Many of the criteria necessary to prove that acetylcholine probably is the efferent and not the afferent transmitter substance have been met.[2,3] Very little else is known concerning the identity of the afferent transmitter substance. Tests to determine whether any substance stimulates the afferent nerve and, thus, possesses afferent transmitter-like activity have been limited to the lateral line organ[4] and electroreceptor.[5] The purpose of the present investigation was to evaluate various chemicals for afferent transmitter-like activity in the mammal, using the compound action potential of the cochlear nerve (AP) as an indirect monitor of single afferent nerve fiber activity. A previous study[6] showed chemicals placed into the perilymphatic space by-passed barriers which hindered passage of substances from the vascular system to the cochlear sensory cell area. Therefore, this study used the scala tympani perfusion technique[6] to examine various chemicals for activity on the AP.

The AP represents the synchronous discharge of cochlear afferent nerve fibers evoked in response to a brief acoustic stimulus. It is an indirect monitor of afferent nerve fiber activity, since a decrease in the magnitude of the AP simply indicates fewer fibers are discharging in synchrony. This could occur in several ways. For instance, external application of the afferent transmitter could induce spontaneous (asynchronous) firing of afferent nerve fibers, making fewer fibers available for synchronous discharge to an acoustic stimulus, yet a chemical could also cause fewer fibers to discharge in any manner (synchronously or otherwise). Either effect would be observed as a reduction in AP magnitude. In this study, an AP reduction obtained by the application of a putative transmitter is considered only as suggestive of afferent transmitter-like ac-

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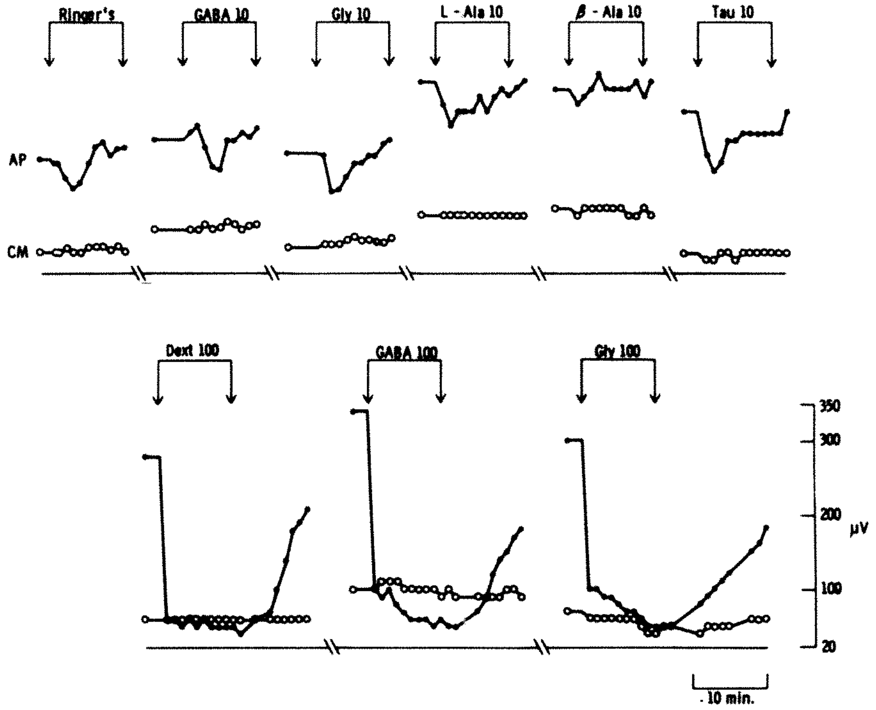

Fig. 1. Effect of GABA and related substances on the AP and CM. Typical plots of AP and CM magnitude evoked by moderate-intensity (75 to 90 dB SPL) tone bursts before, during, and after the perfusion with various solutions are shown. Numbers next to the drug abbreviations refer to the mM concentrations in the perfusion fluid; calibration refers to all perfusions.

tivity, due to these limitations in interpreting changes in AP magnitude.*

METHODS AND MATERIALS

Experiments were performed on pigmented male and female guinea pigs weighing between 300 to 650 gm. Methods used were similar to those described and cited elsewhere.[6] The animals were anesthetized with sodium pentobarbital (Nembutal®, Abbott, 25 mg/kg, I.P., with supplemental doses, I.V.), paralyzed with gallamine triethiodide (Flaxedil®, Davis and Geck, 8 mg/kg, I.V.), and artificially respired. Body temperatures were maintained at 36 to 39 C, right jugular veins were cannulated for drug administration, and middle ear muscles of a majority (36) of the animals were sectioned.

The AP and cochlear microphonic potential (CM) were obtained in response to a 6 kHz tone burst which had a 0.5 msec rise-fall time and a 10 msec duration. To insure maximal sensitivity of the AP to the tested agents, tone bursts were assigned the sound pressure level (SPL) that evoked an AP of at least 200 μV and was not less than 70 decibels (dB) SPL or greater than 90 dB SPL. Stimuli were delivered to the external auditory canal through a closed-tube, hollow ear-bar system. Approximate SPL was measured in dB above the reference of 0.0002 μbar by connecting the ear-bar system to a calibrated microphone and sound level meter. The recording electrode (200 μ enamel-coated silver wire) was placed in a hole in the scala vestibuli of the basal turn and the reference electrode was positioned in the superficial masseter muscle. The recorded voltage was led in parallel through a low-pass filter (2 kHz) and a high-pass filter (3 kHz) to separate the AP and CM, respectively. The AP and CM were then displayed on an oscilloscope and a picture of three superimposed traces recorded from which peak-to-peak measurements were obtained.

The artificial perilymph (Ringer's solution) used to perfuse the scala tympani was the same as that used previously[6] and was composed of: NaCl, 139 mM; KCl, 5.6 mM; $CaCl_2$, 2.2 mM; $NaHCO_3$, 21 mM; gassed with 95% O_2, 5% CO_2; with a resultant pH of 7.2. This solution was an effective buffer for all drugs except 10 mM ATP, which had a pH of 6.2. Drugs were perfused for ten minutes at a rate of 2 μl/min. Osmolality was measured by freezing-point depression using an osmometer (Fiske Assoc., Inc.).

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*Preliminary reports of the results of this work have been made elsewhere.[7,8]

TABLE 1. EFFECT OF AGENTS ON CM AND AP*

	mM	*AP*	*CM*	*n*
Ringer's	—	12±15	6±13	41
GABA	10	−1±9	6±5	3
GABA	100	−55±19	−13±9	4
Glycine	10	−2±9	6±8	3
Glycine	100	−56±27	−20±9	2
Taurine	10	0±7	3±5	4
L-alanine	10	6±6	4±6	3
β-alanine	10	−2±5	3±4	3
Dextrose	25	−29±17	1±4	3
Dextrose	100	−60±22	0±7	4
Acetate	10	−3±11	3±4	3
Glutamate	1	−31±12	5±5	2
Glutamate	10	−84±11	6±5	3
Aspartate	1	−8±4	11±11	2
Aspartate	10	−85±4	6±9	3
Citrate	1	−1±4	15±1	2
Citrate	10	−65±8	0±0	3
Histamine	10	−18±8	−7±5	3
NE	10	−8±12	14±10	3
EPI	10	−2±6	0±0	3
Octopamine	10	12±17	−7±2	3
Tyramine	1	2±2	−3±3	2
Tyramine	10	−93±0	−22±15	3
DA	10	−4±6	0±0	3
5-HT	1	−7±0	7±7	2
5-HT	10	−52±5	−2±3	3
Ringer's-alcohol	—	−16±8	18±10	7
$PGF_2\alpha$	1	−38±5	−5±7	3
$PGF_2\beta$	1	−17±10	37±16	3
PGA_1	1	−34±11	4±6	5
PGE_1	1	−31±22	16±19	3
PGE_2	1	−55±4	3±21	3
ATP	1	−38±18	0±0	3
ATP	10	−93±2	−11±8	3
Bicuculline	1	−2±9	0±0	2
Bicuculline	10	−89±2	−8±7	3
Salicylate	1	−39±15	8±7	3
Salicylate	10	−90±1	5±10	3
Methysergide	1	−94±0	−18±3	3
Methysergide	10	−94	−50	1

*More complete tabular data may be obtained by writing to the senior author.

RESULTS

Observations were made on 158 perfusions in 49 guinea pigs. As a control, Ringer's solution was the first perfusion in 41 of the 49 animals. No second drug solution was tested in the same animal unless the AP and CM recovered during either a 20 minute waiting period or after a wash with a 10 minute Ringer's perfusion. Typical examples of during-perfusion AP and CM responses for a few of the tested substances are shown in Figure 1. Means calculated from values recorded zero to three minutes postperfusion and expressed as percent change from the preperfusion values are shown in Table 1 for each perfused agent, and they were also ranked according to the degree of reduction of AP and CM. All 40 agents tested reduced the AP, with 21 of the responses being greater than 2 SD and 28 greater than 1 SD from the mean of the response to Ringer's.

In contrast to the AP, some agents increased and others decreased the CM relative to Ringer's. Overall, they had little effect on the CM, since only three responses were 2 SD and eight were 1 SD from the mean of the response to Ringer's (Table 1). Some drugs produced a greater change in the high-intensity segment (100 to 120 dB SPL) of the CM input-output function than in the low-intensity segment, the reverse of the AP function. Unfortunately, values for responses to high-intensity tone bursts were obtained for only about half of the perfusions.

The osmolality of the drug solutions was measured. Dextrose was perfused as a control for any osmotic effect. Increasing the concentration of the agents resulted in an increase in osmotic pressure. However, the increase in osmotic pressure was only slightly related to the degree of AP reduction (coefficient of correlation, $r = 0.23$). Dextrose at 25 mM had little effect even though the osmolality (335 mOsm/kg) was close to the highest osmolality of any substance tested at 10 mM; at 100 mM (401 mOsm/kg) the dextrose effect increased (Table 1).

Ringer's Solution. During the ten minute instillation of Ringer's solution, there was very little change in the CM with a reduction in the AP, which usually recovered during the perfusion (Fig. 1). This response has been previously described[6] and may be due to a transient displacement of the cochlear partition. After perfusion, the CM and AP were increased slightly (Table 1).

γ-Aminobutyric Acid (GABA), Glycine, and Other Amino Acids. Perfusion of 10 mM concentrations of GABA, glycine, L-alanine, β-alanine, and taurine had little effect on the AP or CM and were ranked low. When the concentrations of GABA and glycine were increased to 100 mM, perfusion had little effect on the CM but greatly reduced the AP. Dextrose at the same 100 mM concentration appeared to duplicate the response to GABA and glycine. All three ranked high in AP-reducing ability, but only GABA and glycine ranked high in CM-reducing ability (Fig. 1 and Table 1).

Monosodium L-Glutamic Acid and Related Substances. Glutamate, L-aspartic acid, and sodium citrate had very little effect on the AP or CM at a concentration of 1 mM. Increasing their concentrations to 10 mM resulted in solutions which produced rapid reductions in the AP with little, if any, effect on the CM. Glutamate and aspartate ranked close in AP-reducing ability, followed by citrate. Sodium acetate at 10 mM exhibited very little effect on the AP or CM (Table 1).

Monoamines. Histamine dihydrochloride, L-noradrenaline bitartrate (NE), L-epinephrine bitartrate (EPI), DL-octopamine hydrochloride, and dopamine hydrochloride (DA; containing 10^{-5} gm/ml ascorbic acid), had little effect on the AP or CM at 10 mM. Tyramine hydrochloride and 5-hydroxytryptamine creatinine sulphate (5-HT) showed little activity at 1 mM but reduced the AP at 10 mM (Table 1). Tyramine reduced the AP to a greater extent and ranked high overall in this ability, whereas 5-HT ranked low. Tyramine also ranked high in CM-reducing ability.

Prostaglandins (PGs). $PGF_{2}\alpha$-tromethamine 1 mM had little effect on the CM but reduced the AP. The remaining PG solutions contained alcohol, effects of which were examined by mixing appropriate amounts of alcohol with Ringer's and testing the resultant solution (Ringer's-alcohol). Ringer's-alcohol reduced the AP and increased the CM when compared to Ringer's. Taking this into consideration, it appears that $PGF_{2}\beta$ had no effect, PGA_1 and E_1 had a slight effect, whereas PGE_2 had a sizeable effect and ranked high overall (Table 1).

Adenosine - 5′ - triphosphate (ATP). ATP reduced the AP slightly at 1 mM and had a greater effect at 10 mM. The pH of 10 mM ATP was 6.2; however, perfusion with Ringer's with the pH adjusted to 6.2 with 0.5 N HCl had no effect on the AP or CM. At 10 mM, ATP ranked very high in AP-reducing ability and appeared to have some CM-reducing ability at low- and high-intensity levels (Table 1).

Antagonists. Bicuculline methiodide had little effect at 1 mM; however, 10 mM produced a rapid reduction in the AP with little effect on the CM. Sodium salicylate reduced the AP at 1 mM and

10 mM with little effect on the CM. Methysergide maleate (1 mM) reduced the AP and CM. All three agents ranked very high in AP-reducing ability and bicuculline ranked high in CM-reducing ability. Methysergide, at 10 mM, ranked highest in CM-reducing ability and at both 1 mM and 10 mM produced the greatest change in the high-intensity (110 dB SPL) CM (Table 1).

DISCUSSION

GABA, glycine, L-alanine, β-alanine, and taurine were inactive at 10 mM. An earlier study[9] also suggested that GABA and glycine are inactive in the cochlea. The response of GABA and glycine at 100 mM mimicked 100 mM dextrose. This activity, together with the high osmolality, suggest the response to 100 mM glycine and GABA is not dependent on the chemical structure of the tested substance, but instead, is due to osmotic pressure changes in the cochlear structures. Therefore, it appears these substances should not be highly ranked as candidates for the afferent transmitter substance.

The alkaloid bicuculline is considered a GABA antagonist. Others[10] reported that the tertiary bicuculline hydrochloride had no effect on AP and CM at 1 mM. In the present study, the effects of bicuculline were reexamined using the quaternary derivative which is a more powerful GABA antagonist.[11] At 1 mM, bicuculline methiodide was inactive; however, at 10 mM it greatly reduced the AP. In light of the inactivity of similar concentrations of GABA, this response to bicuculline is difficult to explain.

Glutamate and aspartate have been suggested as afferent transmitter substances, due to their large concentrations in the cochlea[12] and because both induced firing in the afferent fibers of an electroreceptor.[5] In the present study, glutamate and aspartate were highly active in reducing the AP. Since acetate was very weak in AP-reducing activity, it appears the action of glutamate and aspartate is probably not related to the substances being carboxylic acids. Citrate, which is a more powerful complexing agent of calcium ions than aspartate or glutamate, was used in the present study and found to be less active in reducing the AP than either glutamate or aspartate. Thus, it appears the reduction in the AP by glutamate and aspartate was not related simply to their ability to complex calcium.

Neither catecholamines nor histamine were detected in the organ of Corti by the fluorescent histochemical technique.[13] This report, together with our data indicating little activity with histamine, NE, EPI, or DA, suggests they are not the afferent transmitter. Tyramine and octopamine, on the other hand, are nonfluorescent monoamines, and tyramine was active in reducing the AP while octopamine, which is structurally related to tyramine, was inactive. This suggests the effects of tyramine are highly dependent on its chemical structure and is the first indication it may be a transmitter substance in the cochlea.

5-HT and methysergide, a 5-HT antagonist, were both found active in reducing the AP. However, synthesis of 5-HT has not been detected in ear or lateral line sense organs.[14] Also, in another study, methysergide exhibited nonspecific effects.[15]

The AP-reducing activity found with ATP is an indication that ATP may be involved in afferent synaptic transmission of the cochlea. On the other hand, others[16] who found ATP active in the CNS correlated that activity with the ability of ATP to complex ions.

In this study, salicylate and PGs were applied intracochlearly and were found to reduce the magnitude of the AP. This demonstrates that the drugs have a direct action on the cochlea and confirms the results of others[17,18] who used an indirect route to apply the substances. Salicylate is an inhibitor of PG synthesis[19] and PGs are thought of as regulators of neurotransmission.[20] Thus, the results indicate a PG is involved in cochlear neurotransmission and suggest salicylate may produce its reduction in the AP by reducing PG synthesis in the cochlea.

In summary, results of this study demonstrate several agents are active in reducing the AP when infused into the cochlea. Mechanisms underlying the action of these substances are speculative at present and must await additional investigation (e.g., studies monitoring single-unit activity) for further elucidation. However, current results seem to eliminate some substances as afferent transmitter candidates and suggest others for further study.

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OTITIS MEDIA WITH EFFUSION

A STEROID AND ANTIBIOTIC THERAPEUTIC TRIAL BEFORE SURGERY

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SUMMARY — Eustachian tube dysfunction has been considered the main factor in the etiology of otitis media with effusion (OME). A short-term systemic steroid therapy, with combined chemotherapeutics, yielded 53.1% cure in 160 children in which OME had been diagnosed, whereas only 12.5% of similar 116 children were cured by chemotherapeutic treatment alone. It is postulated that steroids, acting by a mechanism much similar to the one in the newborn lung, increase the level of a tubal surface active agent, thus enhancing Eustachian tube refunctioning. This combined treatment, we believe, deserves its place as a routine conservative trial before surgery.

Continuous middle ear effusion is apt to be accompanied by a wide range of complications and sequelae.[1-3] The accepted therapy in the beginning is the conservative. If this fails, surgery is resorted to in most cases. Though tympanostomy and insertion of ventilating tubes are widely accepted as an efficient and definitive treatment, complications do arise from their use.[1,4,5] It is sometimes said that the tubes "treat the result much more than the cause of the disease."[6] The common pathophysiologic factor is believed to be characterized in most cases by some degree of Eustachian tube (ET) dysfunction, leading to hypoventilation and deficient drainage of the middle ear.[7]

A wide range of conservative methods of treatment have been implemented with varying success.[8-10] Although systemic steroid therapy is known to be widely used in some institutes, there is a paucity of reports in the literature: Oppenheimer[11] describes his experience with short-term steroid therapy, using 2.25 mg/day dexamethasone in descending dosage. Thirty percent of the children treated that way were cured. Shea[12] discusses a similar treatment of prednisone 12 mg/day for two weeks, which yielded good results.

In our department, short-term systemic glucocorticoid and chemotherapeutic treatment for otitis media with effusion (OME) has been resorted to as an active form of conservative therapy in order to reduce the number of patients requiring surgery. This work is a report of our experience with systemic steroid therapy for OME and a discussion about its mode of action.

METHODS AND MATERIALS

In a series of 276 children, a diagnosis of OME was made. The ages ranged from 1 to 13 years, with most of the cases (about 60%) occurring between 3 to 7 years (Table 1). The male/female ratio was 65% to 35%. Seventy-four and one half percent of the mothers noted deficient hearing in their children. In the rest of the cases, no hearing disturbance was reported.

In all cases, a complete clinical ENT examination was performed, as well as audiometry and tympanometry. Eighteen cases in which an audiologic workup could not be obtained due to age and lack of cooperation were included, based on tympanometry and clinical examination only. A flat (Type B) tympanogram pattern[13] was considered supporting evidence to the presence of the disease.

According to the audiometric examination (obtained for frequencies of 500 to 4000 Hz) the children were divided into three groups:

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TABLE 1. AGE RANGE IN DIFFERENT GROUPS

Group	*0-3 yrs*	*3-7 yrs*	*Over 7 yrs*
A	—	12	10
B	14	128	64
C	—	25	23
Total	14 (5%)	165 (59%)	97 (36%)

Group A: with an air bone gap (ABG) of 0-25 dB.

Group B: with an ABG of 25 to 40 dB.

Group C: with an ABG of over 40 dB.

One hundred sixteen of the children (CH group) were treated with antibacterial chemotherapeutics, ampicillin 50 mg/kg body weight for ten days. One hundred sixty children (ST group) were similarly treated, but were also given prednisone, 1 mg/kg. The dosage was decreased every two days by 5 mg. The treatment was accordingly administered for 10-14 days. At the end of each period of treatment, a clinical and audiologic reevaluation was performed.

The major criterion for success of treatment was a complete return of the tympanogram pattern to normal (Type A)[14] and an audiometric closure of the ABG supported by a clinical appearance of a normal eardrum. When the tympanoaudiometric and clinical improvement was partial, i.e., continuous presence of tympanic retraction and some conductive hearing loss, the patient was classified as "in need of a further treatment." No improvement at all was the third possibility.

RESULTS

Six and nine-tenths percent of the total number of patients of the CH group and 21.4% of the ST group were included in Group A. All these children were in need of no further treatment at the time of reevaluation (Tables 2 and 3).

Group B was the largest (64.3% and 82.8% respectively for CH and ST groups) and the most significant. When treated with chemotherapeutics alone, only 12.5% recovered enough to require no other treatment. Further medical help was needed by 37.5%, while as many as 50% showed no significant improvement at the time of reevaluation (Table 2). When steroids were combined in the chemotherapeutic treatment, about 41% were practically cured. Forty-seven percent showed some improvement and only 12% remained unaffected (Table 3).

Group C comprised 10.3% (CH group) and 14% (ST group) of the patients. When treated with antibiotics alone, none of them were completely cured at the time of reevaluation. Sixty-six percent needed further treatment, while in 33% there was no sign of improvement. When steroids were added, about 33.3% of this group needed no further treatment. Fifty percent were in need of such treatment, and only 16.7% showed no sign of improvement (Tables 2 and 3).

The total number of patients cured by chemotherapeutic treatment was about 17%, as compared to 53.1% in the combination (ST) group. Thirty-eight percent were in need of further treatment at the end of the antibiotic therapy as compared to 36.9% in the other group. No significant sign of improvement was noted in about 45% of all the children treated by chemotherapeutics. When steroids were added, only 10% did not show any improvement.

DISCUSSION

The wide choice of therapeutic methods used for treating OME suggests a complex, multifactored etiology. Paparella[7] emphasized hypoventilation as a dysfunction of primary importance. Sadé[14] tends to blame the mucociliary

TABLE 2. RESULTS OF CHEMOTHERAPY TREATMENT

Group	*A*	*B*	*C*	*Total*
No. of pts.	8 (6.9%)	96 (82.8%)	12 (10.3%)	116 (100 %)
Audiom. and clin. cure	8 (100 %)	12 (12.5%)		20 (17.2%)
Pts. in need of more Rx		36 (37.5%)	8 (66 %)	44 (38 %)
No improve.		48 (50 %)	4 (33 %)	52 (44.8%)

TABLE 3. RESULTS OF COMBINED STEROID AND CHEMOTHERAPEUTIC TREATMENT

Group	*A*	*B*	*C*	*Total*
No. of pts.	36 (21.4%)	100 (64.3%)	24 (14.3%)	160 (100 %)
Audiom. and clin. cure	36 (100 %)	41 (41 %)	8 (33.3%)	85 (53.1%)
Pts. in need of more Rx		47 (47 %)	12 (50 %)	59 (36.9%)
No improve.		12 (12 %)	4 (16.7%)	16 (10 %)

drainage system dysfunction as the major factor responsible for the disease. It is agreed however, that "when the intermittent opening of the ET is impaired, the middle ear behaves like an unventilated gas pocket, absorbing its gases till a subatmospheric gas pressure is formed."[15]

The origin of the effusion thus formed has been extensively reviewed in the literature.[16,17] One of the factors recently stressed as influencing tubal dysfunction is the so-called surface active agent (SAA).[18] The role of surface tension in opening the ET had already been alluded to by Flisberg.[19] Brookler and others[20-22] postulated the existence of surface tension lowering substance in the canine ET. Using the bubble stability technique originally described for demonstration of pulmonary surfactant,[21] a similarity in physical characteristics between this substance and the pulmonary surfactant was shown.[22] The SAA seemed to allow an easier transmission of air and fluid via the ET by lowering the surface tension between its coapting mucosal surfaces.[20]

TABLE 4. TOTAL RESULTS IN TWO GROUPS OF THERAPY

	CH Group Treatment	*ST Group Treatment*
Audiom. and clin. cure	17.2%	53.1%
Pts. in need of more Rx	38 %	36.9%
No improve.	44.8%	10 %

In the presence of nasopharyngeal infection, a significant decrease in the SAA level is noted. It is said to be caused by the proteolytic enzymes produced by the bacteria causing OME due to tubal obstruction.[20] Much emphasis has been placed on the presence of pathogenic bacteria in any part of the tubotympanomastoid functional anatomical unit, "including the nose and nasopharynx."[23,24] Chemotherapeutic treatment alone, however, does not seem to be a definite method for eradicating the infection and curing the patient.

Our results, in fact, confirm this assumption. In the largest and most significant group of patients, i.e., Group B, half of the CH group showed no improvement: the effusion fluid and hearing loss remained unchanged (Table 2). A partial improvement was noted in the rest, but only 12.5% of the children were practically cured by this treatment. Treatment by antibiotics alone then seems to be insufficient.

Rapport et al[18] brought more physiological evidence to the importance of the tubal SAA: they had to use a greater amount of air pressure in order to force open the ET after it had been lavaged with saline. The lack of this washed substance, presumably SAA, appears to prevent a regular opening of the tube and a failure to maintain the balance between the osmotic forces in the tubal wall.[18]

The similarity of the SAA to the pulmonary surfactant was further stressed by Lim.[16] Using the electron microscope, he showed the existence of a lamellar substance (resembling pulmonary surfactant) in the dark cores of granules secreted by the seromucinous glands in the cartilaginous part of the

ET. Based also on cytochemical studies,[16] Lim postulates that this lamellar substance might be the tubal SAA, actively secreted by these dark-granule cells, much in the way that pulmonary surfactant is secreted by the Type II alveolar secretory cells.[25]

A lack of *pulmonary* surfactant is considered a major factor in the etiology of respiratory distress syndrome (RDS) in premature newborns.[26] The resulting high surface tension prevents alveolar ventilation and causes fluid effusion into the alveoli by interfering with the osmotic balance.[27]

In recent years, a smaller incidence of RDS has been noted in cases of prolonged early rupture of the embryonic membrane.[28] In these cases, a high maternal blood level of steroids was noted, due presumably to the stress of the early rupture.[28] It was thus established that a systemic steroid treatment given shortly before an expected early delivery significantly reduced the rate of RDS.[29] The high maternal and fetal blood steroid level, according to Fargier,[30] allows for an enhanced secretion of pulmonary surfactant already stored in the pneumocyte or may act as an enzymatic inductor to its production.

We feel that steroids played a similar part in our cases: 90% of the ST group showed significant clinical and audiological improvement. More than 53% of them required no further treatment. The pathologic condition remained unchanged in only 10% (Table 3). These results are somewhat better than those claimed by Oppenheimer,[11] who obtained a 30% cure in patients treated by steroids with no additional antibiotics.

When the cure rate in the ST group (53.1%) is compared to the percent cured in the CH group (12.5%), the difference is even more striking. There is no clear-cut explanation of this difference in cure rate. Even when some improvement was brought about by the chemotherapeutic treatment,[9] a certain factor was obviously lacking in the way of complete tubal refunctioning. Effusion fluid remained in the middle ear, and the much desired regular opening of the ET did not occur. When steroids were added, on the other hand, a clinical and audiological improvement was obvious.

The antiinflammatory and antiedematous properties of steroids must have contributed to these results, but considering the above mentioned works of Brookler,[20] Rapport et al[18] and others, we tend to believe that steroids might also act by augmenting the production and secretion of the SAA, thus enhancing the return to normal of tubal function.

When a nasopharyngeal infection was a factor in the etiology of the disease, the source of infection might be partially or completely removed by the chemotherapeutic treatment, thus eliminating much of the proteolytic enzymes responsible for the reduction in SAA.[20] The elevated SAA level might act also by restoring the osmotic balance in the tubal wall, thus preventing further effusion[11] and leading to easier refunctioning of the tube.

When the ABG was of a little range, as in Group A, both kinds of conservative treatment proved to be efficient. We tend to conclude that in these cases the final healing stage in the natural history of the disease was encountered. It is possible that the same results might have been achieved with no treatment at all.

An immediate recurrence of the audioclinical signs after the end of treatment seems to indicate some different etiology and leads into a possible surgical approach. In the cases that were finally operated, a mucoid fluid (glue) was found in all the cases. This leads one to consider the mucoid type of OME as being more resistant to steroid therapy than the serous type.

No side effects were noted in our series. It seems that "a few days corticosteroid therapy, when no specific contraindication is present, is unlikely to cause unwanted side effects, except in extreme cases . . . it (corticosteroids) can be given also in no endangering life diseases."[31] We tend to agree, however, with Oppenheimer,[11] that the steroid trial should be of a short duration.

It is to be said that the exact chemical nature of the SAA substance is still uncertain. Some investigators feel that it may be mucoproteins rather than phospholipids. In fact, up to this moment, there is no scientific laboratory evidence to support our hypothesis of tubal SAA production stimulated by glucocorticosteroids.

Whatever may be the exact mechanism by which it acts, we feel that a short-term systemic steroid with additional chemotherapeutic treatment should have its place in the final stages of the conservative therapy before a surgical procedure is implied. An operation requiring general anesthesia might be prevented in a considerable number of children by a treatment which acts in a physiological way to restore tubal function. Much research work has yet to be done; mainly it must be proven that an elevated blood steroid level might directly increase the level of tubal surfactant, thus leading to the way of cure.

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A combined meeting of the Society of Head and Neck Surgeons and the American Society for Head and Neck Surgery will be held May 28-31, 1978 at Hilton Harbour Castle Hotel, Toronto, Canada. For further information contact: Jerome C. Goldstein, MD, Secretary, American Society for Head and Neck Surgery, Division of Otolaryngology, Albany Medical College, Albany, NY 12208, or Elliot Strong, MD, Society of Head and Neck Surgeons, Memorial Hospital, 1275 York Avenue, New York, NY 10021.

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IMMUNOGLOBULIN E IN CHRONIC MIDDLE EAR EFFUSIONS

COMPARISON OF RIST, PRIST, AND RIA TECHNIQUES

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SUMMARY — To investigate the possible role of allergy in otitis media with effusion (OME), the immunoglobulin E (IgE) content of 138 middle ear effusions (MEE) and paired serum samples from patients with chronic otitis media with effusion was determined. The initial 62 paired specimens were assayed for IgE by the radioimmunosorbent test (RIST), while the later 76 paired specimens were assayed for IgE by the paper radioimmunosorbent test (PRIST). When the results obtained by these two techniques were compared, it was noted that the PRIST procedure gave significantly lower IgE values for effusions than the RIST method. When the effusion-to-serum ratios (E/S ratios) were computed from the PRIST data, the E/S ratio was less than one, while RIST data gave an E/S ratio greater than one. The results obtained with the PRIST procedure were confirmed by double antibody radioimmunoassay for IgE. Thus, the PRIST procedure appears to measure the IgE content of MEE more accurately, and the results obtained by this procedure fail to support the concept of allergy as a major causative factor in OME.

Allergy has been considered a major causative factor in chronic otitis media with effusion (OME),[1,2] but laboratory evidence supporting this conclusion has been lacking. Because immunoglobulin E (IgE) has been shown to be the reaginic antibody in man,[3] several studies have been undertaken to determine the IgE content of middle ear effusions (MEE), and conflicting results have been reported. For example, Lim *et al*[4] and Phillips *et al*[5] reported the IgE levels in MEE elevated when compared with matched serum samples, while Reisman and Bernstein[6] and Mogi *et al*[7] found lower levels of IgE in effusion than in serum. The former studies would support the concept of an allergic etiology for OME, while the latter two studies would not. These conflicting results may be due in part to differences in patient populations or in effusion type studied. It should be noted, however, that the former studies[4,5] employed the radioimmunosorbent test (RIST) for IgE quantitation, and recent reports have raised questions regarding the sensitivity and validity of the RIST procedure,[8,9] particularly with respect to the measurement of IgE in secretions. Thus, the possibility exists that the conflicting results in the literature may be due to technical differences rather than population differences.

Since we felt that the IgE levels in MEE were central to the question of allergy in OME, and because our previous study[4] had been done using the RIST procedure, we decided to study this question further by measuring the IgE content of effusions and matching sera by different methods. For this purpose we employed the paper radioim-

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TABLE 1. SERUM IgE CONCENTRATIONS AS DETERMINED BY THE RIST AND PRIST PROCEDURES

Test	*N*	*Mean ± SD (U/ml)*	*Range*
RIST	62	142 ± 290	5-2250
PRIST	76	69 ± 177	2.5-1400

munosorbent test (PRIST),* a recently introduced method that is relatively simple to perform and that has been shown to be more sensitive than the RIST procedure for measuring low levels of IgE.[10] To confirm the PRIST results, selected samples were also analyzed independently by a double antibody radioimmunoassay (RIA).[11] This double antibody RIA has been shown to be a highly sensitive, accurate method for IgE quantitation and has been employed to measure the IgE content of external secretions.[9,12] In this report we compare the results obtained by the PRIST and RIA procedures with the earlier RIST results, and the significance of these findings is discussed with respect to the possible allergic etiology of OME.

METHODS AND MATERIALS

Effusion specimens were collected by a modified Senturia collector and processed in a manner described earlier.[13] A serum sample was obtained at the same time, and both effusion and serum samples were stored at −70C until assayed.

A total of 62 paired samples was analyzed for IgE content by the RIST procedure, and an additional 76 samples were analyzed by the PRIST procedure. Patients whose samples were analyzed by RIST ranged in age from five months to 15 years (mean 5.1 years), and 14 of 61 (21%) had a history of allergy, while those analyzed by PRIST ranged in age from seven months to 12 years (mean 5.4 years), with 13 of the 76 patients (17%) having a history of allergy. While samples were collected throughout the year, most were obtained in late winter and early spring (February-April) of successive years, and the seasonal distribution of the times when samples were collected was the same for the samples analyzed by RIST or PRIST.

The RIST and PRIST procedures were carried out according to the manufacturer's recommendation and appropriate controls and standards were run with each assay. Selected serum and effusion samples (nine pairs) were sent to the Allergy Research Laboratory of the Mayo Clinic, Rochester, Minnesota, where they were assayed for IgE content by the double antibody RIA, as previously described.[11]

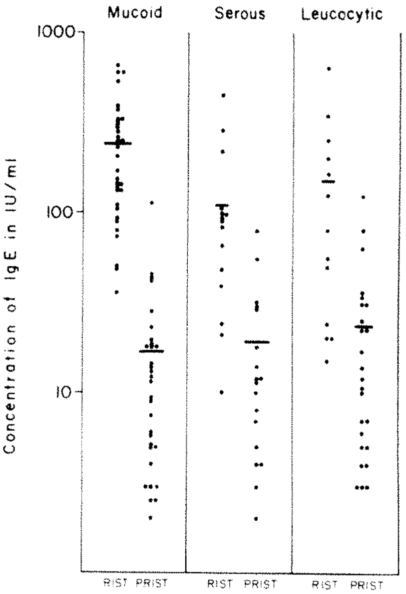

Fig. 1. Scattergram showing the distribution of IgE levels in MEE as determined by the RIST and PRIST methods. The horizontal bar is the mean value for each group.

RESULTS

The concentrations of IgE in serum as determined by the RIST and PRIST are shown in Table 1, and, although the mean PRIST values are lower, there is no statistically significant difference in the mean IgE concentration as determined by the two methods. Because no serum samples were assayed by both procedures, it is impossible to determine the correlation coefficient of the two procedures. However, it appears that the two procedures correlate fairly well for these patient populations and at the levels of IgE found, and the results agree fairly well with published values for normal serum IgE in this age group.[14]

When the IgE concentrations of effusions are compared, there is a marked difference in the results obtained by the two procedures. For each of the effusion types studied, the result obtained

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*Pharmacia Diagnostics, Piscataway, N.J.

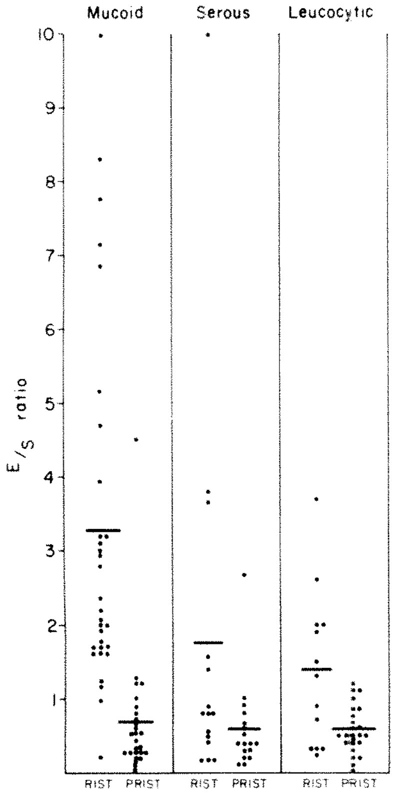

Fig. 2. Scattergram showing the distributions in E/S ratio as computed from RIST and PRIST data. The horizontal bar is the mean value for each group.

TABLE 2. COMPARISON OF IgE CONTENT OF MUCOID EFFUSIONS AS DETERMINED BY THE RIST AND PRIST METHODS

Specimen	*RIST (U/ml)*	*PRIST (U/ml)*
1	260	4
2	50	5
3	250	5
4	444	10
5	160	2
6	115	14
7	315	11
8	288	3
9	172	13
10	276	19
11	342	3
12	60	9
13	225	3
14	64	6
15	425	8
16	798	46
Mean ± SD	265 ± 181	10 ± 10.4

by the PRIST procedure was significantly lower than that obtained by the RIST (Fig. 1). This difference is even more apparent when ratios of effusion IgE to serum IgE (E/S ratio) are compared. The E/S ratios computed from the PRIST data were consistently less than one, whereas with the RIST data the mean E/S ratio was greater than one for all three effusion types (Fig. 2). The difference in the results obtained by the two procedures is of particular significance with respect to the mucoid type of effusion. Using data obtained by the RIST procedure, we found that the IgE content and E/S ratio of mucoid effusions appear markedly elevated, suggesting active production and secretion of IgE by the middle ear mucosa in these patients. The results obtained by the PRIST procedure directly contradicted these results, and so we considered it important to determine which procedure most accurately measures the IgE content of mucoid effusions.

In order to examine this question more closely, 16 mucoid effusion specimens which had been analyzed by the PRIST procedure were assayed for IgE content by the RIST. As shown in Table 2, the results obtained by the RIST procedure were significantly higher ($P < .001$) than those obtained by PRIST. Although these results implied a poor correlation between the tests when used to examine effusion samples, they did not identify which procedure was accurately measuring the IgE content of the effusion. Therefore, effusion and serum samples previously analyzed by the PRIST method were analyzed for IgE content by the double antibody RIA procedure. The results obtained by the double antibody RIA method are shown in Table 3 and are compared with the results obtained by the PRIST

TABLE 3. COMPARISON OF IgE LEVELS IN MIDDLE EAR EFFUSIONS AND SERA OF PATIENTS WITH OME AS DETERMINED BY THE RIA AND PRIST PROCEDURES

	N	*RIA (U/ml)*	*PRIST (U/ml)*
Effusion IgE	9	77.8 ± 94.3*	41.1 ± 34.7
Serum IgE	9	118 ± 128	119 ± 189
E/S Ratio	9	0.75 ± 0.61	1.05 ± 1.44

*Mean ± SD

method on these same samples. As can be seen by inspection of Table 3 there is fairly good agreement between the two procedures, and, indeed, there is no significant difference in the results when the data are analyzed by the paired "*t*" test.

DISCUSSION

The results obtained in this study indicate that there is a lack of agreement between the RIST and PRIST procedures when they are used to determine the IgE content of middle ear effusions. The two procedures yield compatible results with respect to the serum IgE levels, although the results obtained by PRIST tended to be lower than those obtained by the RIST technique. Other workers have shown that the RIST procedure is subject to interference by unknown serum factors which cause the IgE concentration to appear elevated, and that this is particularly true for sera containing low levels of IgE.[8] The PRIST procedure does not appear to be affected by such factors and thus is a more sensitive test for detecting low levels of IgE.[10] The greater sensitivity of the PRIST procedure probably accounts for the difference seen in the serum IgE but cannot fully explain the differences found in the effusion IgE content as determined by the two procedures. If the difference between the tests were simply a matter of the greater sensitivity of the PRIST over the RIST, one might expect to find lower IgE values on the average for the PRIST for both the serum and effusion, but the E/S ratio should be about the same for the RIST and PRIST. The fact that the E/S ratios are significantly different suggests that the two procedures are not measuring the same thing in the effusion samples.

A recent report by Underdown *et al*[9] showed that the RIST procedure may not be applicable for the measurement of IgE in external secretions. Working with colostrum, they found little or no IgE in the whey by double antibody RIA, but when the same samples were analyzed by RIST they found markedly elevated IgE levels. They concluded that there was a factor(s) present in the whey that interfered with the binding of free IgE to the solid phased anti-IgE in the RIST assay which caused the results to be spuriously high. A recent study* compared the sensitivity of the RIST, PRIST and double antibody RIA methods for quantitating IgE in serum and in a variety of external secretions. In this study the results obtained by PRIST and double antibody RIA agreed quite well, while the RIST results correlated poorly and appeared elevated, particularly for secretions. For the effusions we tested, the PRIST and double antibody RIA results agreed fairly closely, leading us to conclude that the PRIST results more accurately describe the IgE content of middle ear effusions than do the RIST results.

The results obtained by the PRIST procedure in this study discourage a belief that IgE-mediated allergic reactions are a major causative factor in OME. In particular, the low E/S ratio values (E/S <1.0) suggest that there might not be active secretion of IgE in the middle ear and thus do not support the conclusions previously published by this laboratory. However, because IgE is biologically active in trace quantities, the presence of even a low concentration of IgE may be significant. Recent evidence has been presented[15] that IgE antibodies to bacterial antigens can be found in the effusions of children with acute suppurative otitis media. Such studies point out the fact that more meaningful information may be gained by looking for specific antibodies in effusions rather than at total immunoglobulins.

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*Gleich GJ, Dunnette SL: Comparison of procedures for the measurement of IgE protein in serum and secretions. Submitted for publication.

In those studies in which specific IgE antibodies have been tested for, the results have not supported the concept of an allergic etiology for OME. Bernstein and Reisman[16] found that out of 200 children who had single or multiple tubal insertions, only 46, or 23%, had histories of allergy. More significantly, when the sera and effusions of eight of these atopic patients were analyzed by P-K skin testing, only three of the effusions gave a positive skin test. Similarly, Mogi *et al*[17] reported that the incidence of IgE antibodies to house dust mites in MEE was nearly the same as the incidence of these antibodies in the serum of the general population. In both of these studies a few patients were found who possessed IgE antibodies in their effusions but not in their sera. Thus, the possibility exists that allergy may play a role in some cases of OME, but it is probably not a major etiologic factor in the development of OME.

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MORPHOLOGY OF TENSOR VELI PALATINI, TENSOR TYMPANI, AND DILATATOR TUBAE MUSCLES

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SUMMARY — The relationships among the paratubal muscles were studied in human fetal and adult Eustachian tubes. That which has, in recent years, been labeled the tensor veli palatini muscle actually consists of two distinct groups of muscle fibers: a medial group, henceforth termed dilatator tubae, and a lateral group, called tensor veli palatini. The latter was found to have no Eustachian tube origin, but was continuous superiorly with the tensor tympani muscle. The dilatator tubae muscle was found to have a tubal attachment. The participation of this muscle system in the normal functioning of the Eustachian tube-middle ear system in man, and the problems inherent in the development of animal models simulating the physiology of the human system, are discussed.

While numerous reports have attempted to present the descriptive anatomy of the musculature associated with the Eustachian tube, few have reported the results of original dissections, and those that have done so often lack congruence. This is especially true of the published descriptions of the tensor veli palatini and tensor tympani muscles. Because of the central role of these muscles in normal Eustachian tube function, an understanding of their structural relations is essential to the development of a more complete understanding of Eustachian tube physiology in normal and diseased ears.

The tensor veli palatini muscle is usually described as taking a wide origin from the scaphoid fossa, the angular spine of the sphenoid bone, and the lateral cartilaginous or lateral membranous wall of the Eustachian tube, or both. The muscle fibers descend anteriorly, medially, and inferiorly to converge in a tendon which rounds the hamular process of the medial pterygoid lamina. The tendon attaches to the posterior margin of the horizontal process of the palatine bone and also inserts into the palatine aponeurosis.[1-7]

Several investigators reported that the tensor veli palatini muscle is anatomically and functionally divided into two distinct planes.[8-11] The more superficial bundle lacks tubal attachment and has a course similar to that commonly described for the tensor veli palatini muscle. The deep bundle is reported to have a direct superior attachment to the Eustachian tube (either the lateral cartilaginous lamina or the membranous lateral wall or both) where it is tendinous on its medial surface. Inferiorly, this bundle is tendinous on its lateral surface and rounds the hamulus (with or without attachment, according to different investigators) to insert into the hard palate, the anterior velum, or the palatine aponeurosis. Significantly, the descriptions provided for the deep bundle are similar to that given for the dilatator tubae muscle by Gray.[12] Gray writes that "the latter [dilatator tubae muscle] arises from the hook of the cartilage and from the membranous part of the tube, and blends below with the tensor veli palatini."[12] The action of this muscle is distinct from that of the tensor veli palatini muscle, and is the active dilation of the Eustachian tube.[12]

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More recent anatomic texts and papers[3,4,13] lack a discussion of this muscle and attribute Eustachian tube dilation to the tensor veli palatini muscle after Rich.[14]

Interestingly, the tensor tympani may also be a component of this multibundled tensor veli palatini system. The tensor tympani muscle is usually described as arising from the cartilage of the Eustachian tube, the sphenoid bone, and the walls of its semicanal.[3,12,13] Within the semicanal, the muscle's tendon courses to the middle ear cavity where it exits the canal, rounds the cochleariform process, and proceeds laterally to insert on the manubrium of the malleus.

Some investigators are not in complete agreement with this "traditional" description and have proposed an intimate relationship of this muscle with the tensor veli palatini. According to Politzer:[15]

> The tendon of the tensor tympani, which can be traced some distance in its canal, lies in a sheath in its free course (Toynbee's tensor ligament). According to Henle, this sheath is connected to the tendon by considerable prolongations of connective tissue. The anterior portion of this muscle is sometimes united with the tensor veli palatini, either directly or by fibrous tissue (L. Mayer).

Proctor[16] described an "intermingling" of fibers from the tensor veli palatini and tensor tympani muscles "on the internal aspect of the sphenoid spine" and Lupin[17] reported:

> Anterior fibers of the tensor palatini muscle run upwards and backwards crossing the Eustachian tube on its lateral and superior surface, receiving a slip from the base of the sphenoid and then continuing backwards as the tensor tympani muscle.

In addition, Wolff[18] cited Rüdingen, Von Tröltsch, and L. Mayer as having suggested a connection between the tensor veli palatini and tensor tympani muscles. However, Graves and Edwards[6] failed to find direct continuity between the two muscles and proposed acceptance of the more traditional separatist position.

Evidences gleaned from other sources support the observation that the two tensor muscles are continuous. Both muscles have a common embryonic origin from the mandibular arch and share a common motor innervation via the mandibular branch of the trigeminal nerve.[17] The tensor tympani is observed to respond during "movement patterns which involve the muscles of the pharynx and larynx such as yawning, laughing, swallowing, and coughing."[19] Further, in presenting the results of a Eustachian tube physiology study, Holborow[20] wrote:

> It is suggested that both tensor palati and tensor tympani are functionally tubal muscles and might, perhaps, be termed single "extrinsic muscles of the ear." Together they largely control tubal opening.

Kamerer,[21] reporting on an electromyographic study of the two muscles in response to a variety of stimuli in humans, stated that "the concept of a single tensor muscle, with two anatomic divisions, a common nerve supply, and parallel function is therefore submitted."

While much confusion and disagreement exist with respect to these paratubal muscles, there is clearly sufficient evidence to suspect that the tensor veli palatini, dilatator tubae, and tensor tympani muscles are continuous and, in fact, the same muscle. Their possible role in tubal function, physiology, and consequently middle ear function dictates the need for a comprehensive investigation of the anatomic relations of this muscle system. The present paper addresses this problem and attempts to clarify the aforementioned areas of dispute.

METHODS AND MATERIALS

Three grossly normal human fetal specimens, approximately 19 weeks of age as determined by reference to the charts developed by Streeter,[22] were prepared for study by light microscopy. The details of the preparation procedures were previously published by one of us.[23] Serial cross-sectional and longitudinal views of the Eustachian tube-middle ear system were obtained for the three specimens. In addition, one side from each of six human cadaver heads was studied. The cadaver specimens were all adult, as determined by the complete eruption of dentition, and consisted of the following: one Negro male, one Negro female, three Caucasian males, and one Caucasian female. A block of tissue containing a portion of the nasopharynx, the Eustachian tube, and the middle ear was excised from each head. Both lateral and medial dissection approaches to investigate the continuity between tensor veli palatini and tensor tympani were

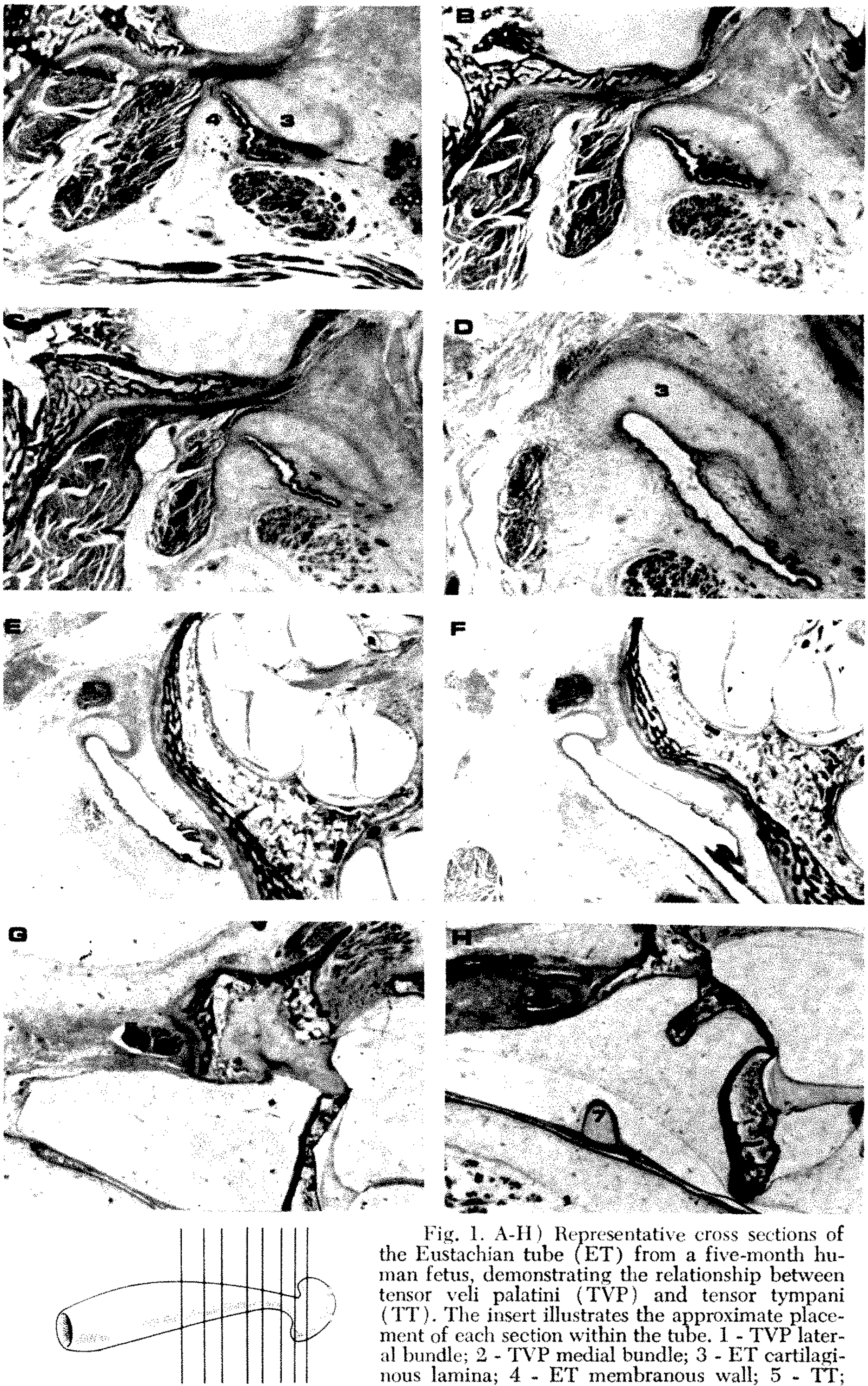

Fig. 1. A-H) Representative cross sections of the Eustachian tube (ET) from a five-month human fetus, demonstrating the relationship between tensor veli palatini (TVP) and tensor tympani (TT). The insert illustrates the approximate placement of each section within the tube. 1 - TVP lateral bundle; 2 - TVP medial bundle; 3 - ET cartilaginous lamina; 4 - ET membranous wall; 5 - TT; 6 - levator veli palatini m.; 7 - malleus (original magnification: A-C, E, F - X30; D, G, H - X60).

employed. Extensive photographic documentation of the procedures and observations was made.

RESULTS

The observations presented in this section were obtained on the basis of the descriptive data recorded from the study of the human fetal specimen group and the human adult specimen group. The results of the histological portion of this investigation will be presented first, followed by the presentation of the gross dissection data. The third subsection attempts to pool analogous information from both parts of the study to present a detailed morphological delineation of the paratubal musculature.

Histology: Human Fetal Specimens. A series of photomicrographs proceeding posteriorly through a representative human fetal Eustachian tube depicts the relationship among the paratubal muscles (Fig. 1). The tensor veli palatini muscle, immediately lateral to the membranous tubal wall, has traditionally been described as a single unit. However, the organization of this muscle is somewhat more complex than was previously thought (Fig. 1A). The tensor veli palatini muscle is divided into two morphological planes or groups of muscle fibers: a medial bundle and a lateral bundle. The medial fibers have a superior attachment into the posterior one-third to one-half of the lateral membranous wall of the Eustachian tube. Some variability in the extent of attachment was noted. No attachments to the lateral cartilaginous lamina were observed at any point in any fetal specimen studied. Inferiorly, the muscle fibers become tendinous, round the hamulus, and attach to the posterior margin of the palatine bone and into the anterior velum. The lateral group of fibers was separated from the medial group by a line of connective tissue and was observed to have no direct tubal attachment. Inferiorly, this group of fibers has attachments similar to those of the medial group. In addition, some intermingling of fibers between the medial group and the lateral group was identified.

Figures 1B-H illustrate the superior or posterior course of the lateral fiber group. This group becomes partitioned into a small, rounded, superior bundle and a larger, ovoid, inferior muscle mass. Fibers of the inferior bundle were found to attach to the cranial base. Further posteriorly, the small muscle mass became tendinous as it entered the semicanal of the tensor tympani muscle. Some muscle fibers were found within the tendinous mass in the semicanal. Further, some small slips of muscle fibers were observed to enter the tendinous bundle apparently originating from the walls of the semicanal itself. However, before exiting the semicanal, the tensor tympani again became completely tendinous. This muscle then assumed its usually described lateral course at the cochleariform process and inserted into the manubrium of the malleus.

Gross Anatomy: Human Adult Specimens. Figure 2A demonstrates the gross relationship between the lateral (reflected) and medial (immediately adjacent to the membranous tubal wall) fiber groups of the tensor veli palatini muscle. As in the fetal specimens, the medial fiber group was observed to have an attachment to the lateral membranous wall of the Eustachian tube but no direct cartilaginous relationship. The lateral group was reflected from the underlying medial group with some difficulty. However, two separate planes of fibers were identifiable. The inferior (anterior) terminations of both groups were those noted for the fetal specimens. The observations reported here were consistent for all of the specimens studied.

Figure 2B illustrates the continuity, on the lateral surface, of the lateral fiber group of the tensor veli palatini muscle and the tensor tympani muscle. The more anterior fibers were found to have a cranial-base attachment to the sphenoid bone (scaphoid fossa to sphenoid spine). However, the more posterior tendinous fibers were followed into the semicanal of the tensor tympani with no intervening cranial-base insertion noted. Additional small slips

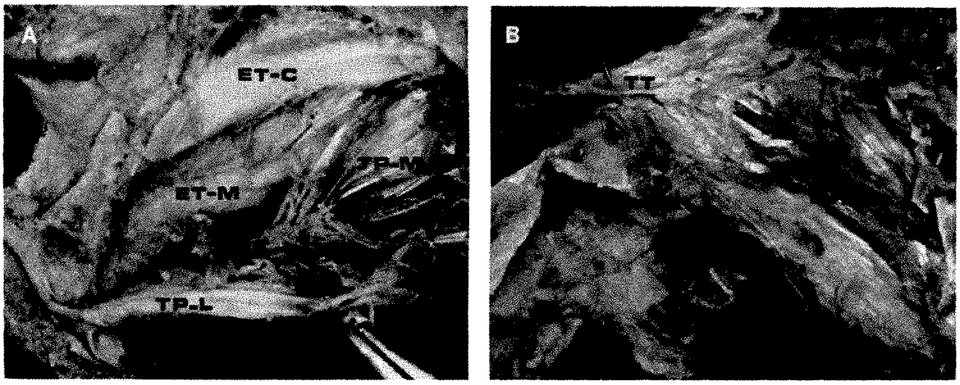

Fig. 2. A) Lateral view of an adult Eustachian tube/temporal bone specimen, demonstrating the division of tensor veli palatini into a lateral fiber group (reflected, TP-L) and a medial bundle (TP-M) and the latter's attachment to the membranous tubal wall (ET-M). Note the lack of attachment to the lateral cartilaginous lamina (ET-C). B) Lateral/superior view of an adult specimen illustrating the continuity between tensor veli palatini (TVP) and tensor tympani (TT).

of muscle fibers were found to originate from the walls of the semicanal and from the tubal cartilage. These merged with the continuing fibers from the tensor veli palatini muscle to form the tensor tympani muscle. Thus, the tensor tympani and the lateral fiber group of tensor veli palatini appear to be one continuous system with an intervening fibrous band joining the two areas of actual muscle fiber. Tensor tympani became tendinous once more as it approached the cochleariform process.

Muscle Morphology. The lateral fiber group of the tensor veli palatini muscle is of an inverted triangular design, taking origin from the scaphoid fossa, the spine of the sphenoid bone, the tendon of the tensor tympani muscle, and the entire lateral osseous ridge of the sphenoid sulcus. No muscle fibers were found which were directly related to the Eustachian tube at either the cartilaginous or membranous walls. Rather, the raised lateral edge of the sphenoid sulcus provided a linear attachment for the descending muscle fibers. These fibers originated lateral to and perpendicular to the tube for its entire course from the osseous-cartilaginous junction to the nasopharyngeal orifice. The fibers descended anteriorly, laterally, and inferiorly to converge in a tendon which rounded the hamular process of the medial pterygoid lamina about an interposed bursa. This fiber group then inserted on the posterior border of the horizontal process of the palatine bone and into the anterior portion of the velum.

The more posteroinferior muscle fibers of the lateral bundle of the tensor veli palatini muscle lacked any osseous cranial-base insertion, but rather extended into the semicanal of the tensor tympani muscle. Here, the latter group of fibers received more medial slips of muscle fibers originating from the tubal cartilage and sphenoid bone. The muscle masses then converged to become attached to a tendon which coursed within the semicanal to the cochleariform process. This arrangement of muscle bundles and tendon gives the tensor tympani its bipinnate form. The tendon made a right-angle turn to cross the tympanic cavity and insert into the manubrium of the malleus. Within the canal, the tendon is invaded by a few decussating muscle fibers throughout its length. Figure 3 presents the relationship of the lateral bundle of the tensor veli palatini muscle and the tensor tympani muscle in a highly schematized form. The drawing is distorted about the tensor tympani tendon by medial rotation of the anterior tensor veli palatini segment and lateral rotation of the posterior middle ear segment so as to allow for planar

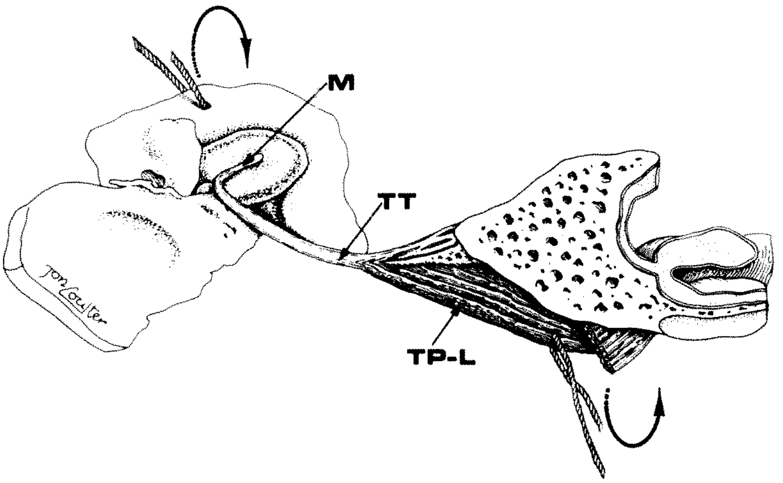

Fig. 3. A schematic superior view of an adult specimen, rotated somewhat (as indicated by the arrow), demonstrating the relationship between the tensor muscles. Note that additional fibers from the wall of the semicanal are added to the lateral bundle of tensor veli palatini (T P-L) to form tensor tympani (TT). M - Malleus.

representation of the two opposing sides. The continuity between the lateral bundle of the tensor veli palatini muscle and the tensor tympani muscle is clearly defined.

The medial bundle of the tensor veli palatini muscle lies immediately adjacent to the lateral membranous wall of the Eustachian tube and medial to the lateral group of tensor veli palatini muscle. It takes its superior origin from the posterior one-third of the lateral tubal wall. No fiber attachment to or blending with the perichondrium of the lateral cartilage was observed. The fibers descend rather sharply to enter and blend with the fibers of the lateral group of the tensor veli palatini muscle, confounding attempts to trace the fibers of this muscle group. Some fibers of this group, however, were observed to terminate on the posterior border of the medial pterygoid lamina.

DISCUSSION

The observations presented in the previous section of this paper clearly support the existence of a single lateral paratubal muscle mass which is incompletely divided into three functional bundles. The three bundles probably have differing functions, although all are most likely related to the function of the Eustachian tube-middle ear system.

For purposes of designation, the three muscle bundles are referred to by their classic names: the tensor veli palatini, tensor tympani, and dilatator tubae. The term "dilatator tubae" was chosen over the more recent names for this bundle (i.e., deep, medial) as it does have precedence in the anatomic literature and inherently describes the action of this bundle.

Our description of the dilatator tubae muscle bundle closely agrees with the descriptions presented by Gray.[12] It originates from the entire membranous wall of the posterior one-third to one-half of the membrano-cartilaginous tube. Although Ross[10] and Deuschle et al[24] reported that fibers of this medial bundle were attached to the lateral cartilaginous laminae, no such attachment was observed in the present investigation for either adult or fetal specimens. The fibers of this bundle descend obliquely with respect to the tube to intermingle with those of the tensor veli palatini muscle bundle. The exact disposition of these fibers within the tensor veli palatini could not be traced in the adult specimens and two individual tendons could not be identified at the hamulus as was suggested by previous investigators.[8,10,24] Rather, it is submitted that the fibers of this muscle become directly continuous with those of the tensor veli palatini and lose their identity within that muscle mass. Since this muscle bundle is the only one to have direct tubal attachment, it should be considered to be the active tubal dilator as described by Gray[12] and others.[8,10,23] This bundle may serve to draw the membranous tubal wall laterally and inferiorly.

The tensor veli palatini muscle mass took its origin from the scaphoid fossa, the sphenoid sulcus, the angular spine, and the tendon of the tensor tympani. No tubal origin was defined for any of the specimens. The fibers descended from the cranial base to intermingle with those of the dilatator tubae bundle and to converge upon a tendon which rounded the hamular process to insert upon the palatine bone and become continuous with the palatine aponeurosis. While Rich[14] described an attachment of these fibers to the hamulus in the dog, no comparable attachment was observed in the present study. This agrees with the results reported by Ross[10] for man. A number of fibers do appear to insert into the medial pterygoid lamina on both the lateral and medial aspects as was described by Rood.[8] The action of this muscle bundle is unknown, although it may serve to tense the anterior portion of the velum or to assist the dilatator tubae in tubal dilation by serving as a stiff strut against which the action of the dilatator tubae may be enhanced.

The tensor tympani is described in the present paper as bipinnate muscle. The most medial group of fibers arise from the sphenoid bone and superior tubal cartilage. The lateral group of fibers arise as a continuation of the most inferoposterior fibers of the tensor veli palatini, which lack bony attachment, but rather extend lateral to the tube and into the semicanal to join the tendon of the medial fibers. This tendon bears many interspersed muscle fibers for almost its full course to the tympanum and just anterior to the cochleariform process. These descriptions are in full agreement with those provided by Lupin[17] and view the muscle as a direct continuation of the tensor veli palatini rather than as an intermingling of fibers of separate muscles.[6,9] This muscle bundle may serve to move the malleus and consequently the tympanic membrane medially, thus tensing the latter structure. More removed from the classic description of the action of this muscle is the postulated reflex hypertonic influence on the tensor veli palatini.[20,25] While the anatomic descriptions provided in the present communication are compatible with this mechanism, further comment should await the results of future investigations on the physiology of this system.

Interestingly, much of what is accepted with regard to Eustachian tube function has its basis in experimental work with various carnivores and subhuman primate species.[14,25-30] The animal chosen for early investigations was the domestic dog (*Canis familiaris*), while more recently the Rhesus monkey (*Macaca mulatta*) has been the animal of choice. The results of experimentation with these species has been all too readily extrapolated to the human condition, often without clear definition of the anatomic congruencies between the species. In this regard, it is of some import that the species *Canis familiaris* and *Macaca mulatta* have different paratubal muscle constructions than those reported here for man.

Of particular importance is the lack of a dilatator tubae or medial bundle of the tensor veli palatini muscle system. Rather, for the Rhesus monkey and dog, the tensor veli palatini is singular in nature and takes its origin directly from the lateral membranous wall of the tube.[31,32] In these animals, the tensor veli palatini muscle appears to be solely responsible for tubal dilation.[14,30] In humans, on the other hand, the tensor veli palatini lacks tubal insertion, and the dilatator tubae muscle bundle appears to be responsible for tubal dilation. The extrapolation of Rich's investigations with the dog to humans may have been responsible for the acceptance of the tensor veli palatini dilating mechanism reported for man and the neglect of the dilatator tubae muscle in those descriptions which followed.

Further, in these experimental animals, no direct continuity between the tensor veli palatini and tensor tympani muscle bundle is established. For the dog, the tensor tympani is wholly intratympanic. However, a tendon bearing some muscle fibers of the tensor veli palatini does approach the tympanum in association with the branch of the mandibular division of the trigeminal nerve which innervates the tensor tympani muscle.[32] The Rhesus monkey Eustachian tube is completed laterally by a thick fibrous blanket to which the tensor veli palatini is inserted more anteriorly and the tensor tympani muscle fibers more posteriorly. No intermingling or extension of tensor veli palatini fibers to the tensor tympani muscle was noted.[31]

These comparative descriptions suggest that the human tensor veli palatini-tensor tympani continuity is the result of secondary fusion of the two independent muscles. On the other hand, the dilatator tubae-tensor veli palatini relation most probably resulted from an incomplete fission of the tensor veli palatini muscle. Future work on this region in pongid species may verify this postulated phylogenetic development.

The significance of these interspecific differences with respect to the function of the Eustachian tube-middle ear system is, at present, unknown. However, caution should be employed in attempting any extrapolation from the result of studies with experimental animals to man.

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FIFTH BRITISH ACADEMIC CONFERENCE IN OTOLARYNGOLOGY

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Ann Otol 87:1978

NEOMYCIN OTOTOXICITY

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SUMMARY — A case of oral neomycin ototoxicity is presented, followed by a summary of known cases in the English literature. While it is known that neomycin is concentrated in the inner ear fluids, at the present time the biochemical basis of its ototoxic effect has not been definitively elucidated. High frequency audiometry can aid in the early detection of the onset of neomycin-induced deafness. Dialysis has a limited but useful role in preventing neomycin ototoxicity.

The ototoxic properties of neomycin are well-known. However, whereas most of the earlier reports of neomycin ototoxicity were concerned with its parenteral administration, more recent case reports have also noted ototoxic effects with the irrigation of wounds, joints, the colon, the mediastinal and the pleural cavities; with cutaneous application; when inhaled as an aerosol; and with the oral usage[1-8] of neomycin. While vertigo and hearing loss have been reported following the topical administration of neomycin ear drops,[9] the topical application of neomycin to the external ear canal or to the middle ear is considered by most to be innocuous with only occasional hypersensitivity skin reactions.

Neomycin, first isolated in 1949, was found to be a potent bactericidal agent effective against the majority of Gram positive and Gram negative bacteria. However, the damaging effect of neomycin on the kidneys, via proximal tubular necrosis, led to the general abandonment of neomycin's parenteral usage except, perhaps, in certain severe infections. Some recovery of renal function following discontinuation of neomycin usage could be expected in the kidneys but the ototoxic effect was not recoverable. Other, rarer, adverse effects of neomycin include peripheral neuropathy, blood dyscrasiae, allergic reactions and respiratory arrest secondary to intraperitoneal or intrapleural administration.

The basis of the present report is a woman who became totally deaf following the administration of a total of 91.5 gm of neomycin orally.

CASE REPORT

The patient was a 54-year-old Caucasian female, admitted with a diagnosis of bilateral vesicoureteral reflux, who underwent surgery for the reimplantation of her scarred ureters. Postoperatively, she experienced a hypotensive episode and then developed progressive renal and hepatic failure. No obstruction of her ureters could be identified, and both her liver enzymes and liver biopsy indicated an obstructive-type jaundice. In an effort to alleviate her hepatic coma, she was given a total of 91.5 gm of neomycin orally over a period of 31 days (56 gm over days 1 to 5, 6 gm over days 16 and 17 and 29.5 gm over days 23 to 31), during which time her creatine varied from 3.8 to 6.6. The serum neomycin level on day 31 was 7.5 mg/ml. She also received gentamicin (a total of 330 mg IV over days 15 to 25), tetracycline, sodium cephalothin, nalidixic acid, carbenicillin, and furosemide (160 mg orally). On day 29, it was first noted clinically that her hearing was diminished. On day 32 an otolaryngologic physical examination was negative; audiologic testing revealed a

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TABLE 1. KNOWN CASES OF DEAFNESS RELATED TO ORAL ADMINISTRATION OF NEOMYCIN

Author	*Age*	*Indication*	*Contributing Factors*	*Total Dose (gm)*	*Estimated Period of Treatment (Days)*
Last & Sherlock[1]	51	HC	BUN 53	560	140
Halpern & Heller[2]	40	HC	Esophageal varices	600	70
King[3]	1½	Gastro-enteritis	Inflamed mucosa	2	4
Greenburg & Momary[4]	53	Perforated diverticulus	Leakage into peritoneum	46	11
Gibson[5]	11	Ulcerative colitis	Ulcerated mucosa	7600	300
Ruben & Daly[6]	45	Preop. bowel cleansing	Intestinal obstruction & preop. anuria	11	2
Berk & Chalmers[7]	49	Hepatic precoma	Esophageal varicies	2500	485
	47	HC	Portacaval shunt 2 yr prior	800	640
	39	HC	Serum creat. to 2.1	1500	335
	66	Hepatic enceph.	Serum creat. to 14	500	243
	60	Hepatic enceph.	Portacaval shunt 2 yr prior; Serum creat. to 4.5	1000	890
Kalbian[8]	55	HC	None	1750	790
Ward & Rounthwaite	54	HC	Serum creat. to 6.6	91.5	31

HC - Hepatic coma; Preop. - Preoperative; Enceph. - Encephalopathy; Creat. - Creatinine.

moderate to moderately severe sloping, sensorineural hearing loss bilaterally; and special testing was suggestive of cochlear pathology for the right ear and retrocochlear pathology for the left ear. Reevaluation on day 53 revealed rapid deterioration to a profound bilateral hearing loss. Vestibular function was normal. When retested 11 months later there had been no return of auditory function.

DISCUSSION

By 1957 it had been demonstrated that oral neomycin, by decreasing the ammonia-forming organisms in the gastrointestinal tract, was useful in the control of the neuropsychiatric manifestations of hepatic failure. Since then, in addition to its established role of cleansing the bowel flora prior to surgery, it has been widely used for both the management of the acute phase of hepatic coma and also as a long-term prophylactic measure in chronic portal encephalopathy.

Initially, it was believed that neomycin was not absorbed from the intestine; however, it subsequently was discovered that up to 3% of an oral dose was absorbed.[10] Last and Sherlock[1] first reported a case in 1960 of deafness related to the use of neomycin orally in a patient with portal encephalopathy. Since then, 11 other cases of deafness due to oral neomycin have been reported (Table 1). Of these 12 cases, Berk and Chalmer's[7] were the only ones to report a case in which the serum neomycin level was measured before the onset of ototoxicity. They reported serum levels of 2.4 to 4.8 mg/ml, when the patient's creatinine was 8 to 14 mg/100 ml and he was receiving 3 gm of base antibiotic per day. Unfortunately, this patient received paromomycin in addition to his neomycin in an attempt to control his hepatic encephalopathy. It thus appears that the present case is the only one where serum neomycin levels have been performed where oral neomycin alone can be reasonably implicated.

While renal impairment is not a prerequisite for the development of ototoxicity,[11] neomycin in patients with normal renal function is rapidly excreted in the urine, and thus renal failure tends to increase the circulating level of neomycin.

There is no critical dose below which toxic effects need not be feared.[11] Although it was originally felt that the total dose over time which causes damage was essentially constant, more recent work[12] has shown this to be a naive assumption that oversimplified the complex matter of chronic drug administration, absorption, penetration to the pertinent site, cumulation, excretion and fluctuating sensitivity to its action.

Pathophysiology. Neomycin is concentrated and retained in the inner ear fluids, with substantial amounts of neomycin still being present in inner ear fluids 24 hours after a single intramuscular dose.[13] ($T_{1/2}$ in the serum is approximately three hours following an IM injection.)[14] This helps to explain why the cochlear microphonics continue to decrease after neomycin is discontinued, why a latent period usually exists prior to the onset of symptoms,[11] and why even minimal absorption and low serum levels may be harmful when present over a period of months or years.[7] Hearing loss may or may not be heralded by tinnitus or a feeling of fullness in the ear;[13] vertigo is not a common symptom and, in many cases, does not appear at all. Hearing for high tones is usually affected first[13] and, in most cases, hearing loss is complete in three months and irreversible thereafter.[11]

A current theory of intoxication[15] states that the neomycin stays in the inner ear fluids longer than in the blood because of slower elimination and that, among the cochlear cells, the more active ones appear to be more sensitive to the antibiotic. Thus, the ototoxic product is carried by the blood stream to the peri- and endolymph where it is retained longer than in the blood because of the slow elimination by the stria vascularis. The resorption of this ototoxic material is greatest in the stria vascularis of the basal coil, where its toxic effect slowly makes itself felt. In consequence of this, the resorption diminishes, the process of elimination lasts longer, and the structures of the internal ear are exposed to the toxic product for a longer time. The sensory cells that are most important, be it because of their greater activity or because of their more delicate function, are affected first, beginning with the most medial and extending towards the more lateral ones, and from the basal towards the apical areas. With further intoxication more of the stria vascularis is affected, with reduced absorption, prolonged duration of elimination and longer exposure to the toxic product. Thus, more sensory cells are affected and, following repeated and prolonged exposure, less sensitive cells are affected as well. After the disappearance of the sensory cells, the whole structure of the organ of Corti collapses slowly and the corresponding nerve fibers and ganglion cells degenerate.

Spoendlin[16] found that the numerical ratio of innervation density of inner and outer hair cells is 20 to 1; each inner hair cell is innervated by about 20 independent afferent neurons, whereas, at the level of the outer hair cells, each afferent neuron is connected to about ten outer hair cells. This invites the supposition that the inner hair cells have a higher metabolic activity and would thus be affected first by ototoxic agents. This theory has been substantiated by the histological finding in a human[17] that neomycin causes degeneration of the inner hair cells and, to a lesser extent, the outer hair cells; although Lowry,[38] in a more acute case of neomycin ototoxicity in a human wherein "hair cell nuclei were counted as being present even though markedly abnormal," found a larger actual disappearance of outer hair cell nuclei. In both cases, the stria vascularis showed some degeneration in the basal turn opposite the hook, a finding that is in keeping with the area's higher metabolic activity as evidenced by the denser innervation of the outer hair cells in the basal coil than that in the apical coil,[16] and by the fact that oxygen consumption has been found to be greater in the basal than in the apical areas.[19] Lesser degrees of degeneration were evident in the pillars and, to a minor degree, in Deiters' cells. The spiral cell ganglion count was felt to be normal, and the maculae and cristae were normal; this sparing of the vestibular labyrinth is in agreement with clinical findings that vertigo is not usually a common symptom of toxicity.

Spoendlin's[20] studies with neomycin showed that whereas the nerve endings (which do not synthesize protein to any extent) were not damaged, the structures which were most affected within the damaged sensory cells were the nuclei and the ribosomes, and both these organelles do synthesize protein. It has been suggested that the primary effect of neomycin was an alteration of the attachment of aminoxyl-sRNA (transfer RNA) to the ribosomes; when this alteration is maximal, peptide synthesis can no longer occur. Thus, it may be that neomycin may act upon the sensory cells to produce toxic changes in much the same way as it exerts its antibacterial activities, namely, by an inhibition of protein synthesis. More recently, Brown and Daigneault[21] have noted that neomycin appears to have a pharmacological action on the efferent synapse which occurs before extensive ototoxicity develops. This could be explained by Schacht's[22] suggestion that neomycin acts by affecting biochemical events or ion transport in the mammalian cell membrane, as evidenced by his finding of an inhibition of both calcium binding and the turnover of membrane polyphosphoinositides. Thus, it appears at present that the biochemical basis of neomycin ototoxicity has not been fully elucidated, and that further study is needed before the actual underlying mechanism becomes generally accepted.

Clinical Usage of Neomycin. While it is impossible to avoid the ototoxicity of neomycin when it is used, certain therapeutic modifications have been advocated in an effort to minimize neomycin's adverse effects. Neomycin glucuronate is equal to neomycin sulfate in its antibacterial effect, and the neurotoxic effect of the former is noticeably less. It has also been found that, in the acute test, the pantothenate form has a less toxic effect than the sulfate, due to the reduction in the calcium binding ability of the antibiotic; in the chronic experiment the pantothenic acid also had a protective action on organs derived from ectoderm, especially the vestibule and cochlea. Other factors to keep in mind include ototoxic synergism, wherein previous treatment with an ototoxic antibiotic may render the spiral organ more susceptible to damage by subsequent treatment with another antibiotic, and the fact that sensory cells sensitized by a chemical noxious agent, such as neomycin, are more susceptible to mechanical trauma, for example, intensive noise.

The concomitant or successive use of two or more ototoxic drugs, along with renal immaturity, increasing age and preexisting inner ear disease, all predispose the patient to the development of ototoxicity. Renal failure should be assessed before and during treatment and, if possible, patients in renal failure should be treated in accordance with Kunin and Finland's[14] regimen, whereby the dose is reduced on a scale related to the renal function. Though neomycin is only moderately dialyzable, as low blood levels preclude the removal of large amounts of the drug, in cases of inadvertent overdosage, for example, when an oral dose is given intramuscularly by mistake, prompt and prolonged hemodialysis can be expected to remove a portion of the drug, thus decreasing the risk of ototoxicity, especially in cases of renal failure.

In cases where neomycin is used, frequent audiometric testing would appear to offer some warning prior to the onset of deafness. Jacobson *et al*[23] found that, by using high frequency audiometry, marked hearing level changes were detected 41 to 76 days before detection with conventional audiometry in four out of seven patients, and that these changes preceded the onset of tinnitus, in those patients who did experience tinnitus (four out of six), by 7 to 56 days. This progression of hearing loss was most apparent first in the frequency range from 9 through 13 kHz, before any deterioration of the hearing level occurred for the frequency above 13 kHz.

While there is no critical dose below which the toxic effects need not be feared,[11] it has been noted in the treatment of liver failure that there is an adequate clinical response with no more than 6 gm of neomycin daily, and rarely does significant additional improvement follow with a higher dose.[1]

Our experience, and that of others, points to the desirability of finding another agent that does not have the ototoxic characteristics of neomycin for use in the long-term treatment of hepatic encephalopathy. Kanamycin is, in general, slightly less ototoxic than neomycin,[13] although it yields similar serum levels; there is no data on the comparative toxicities of these levels during long-term administration to cirrhotic patients.[7] Tetracycline presents the danger of liver toxicity and decreased anabolism, especially in patients with renal failure, and neither it nor the sulfonamides are very effective bowel flora suppressants.[7] Perhaps the use of lactulose (Cephulac®, Duphalac®), a nonabsorbable synthetic polysaccharide that maintains a low colonic luminal pH resulting in less absorption of ammonia, is currently the best method of treating hepatic encephalopathy.

Although the connection of deafness with neomycin in this case has not been definitely proven, the known ototoxicity of the drug, demonstrable serum levels and appropriate type of sensorineural impairment tend to implicate neomycin as the causative agent.

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AIR CALORICS

A TECHNIQUE AND RESULTS

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SUMMARY — A major problem with air calorics appears to be one of technique. A pilot study led to the design of irrigating tips which allow consistent air presentation and simultaneous measurements of irrigating temperature at the delivery orifice (adding a second sensor). Preset temperatures of 24 C and 50 C in our system yielded air equilibration mean temperatures of 27.4 C and 45 C at the delivery orifice during testing. A normal study was carried out at these temperatures with an air flow of six liters per minute for 60 seconds. The range of caloric responses, mean maximum speed, and standard deviation are comparable to values previously reported with water stimulations. Statistical testing indicated no difference between ears for either warm or cold. Also, there was no significant difference for warm versus cold responses. We have performed over 2000 clinical examinations that incorporate this technique with satisfactory results and remarkable acceptance by the patients. The normal or "standard" probe size has been found to be adequate for the majority of the clinic population.

The bithermal caloric test of Fitzgerald and Hallpike[1] has been performed in thousands of patients worldwide for evaluation of vestibular function. Several investigators[2-5] have contributed to the development of instruments which allow adequate performance of the test with air.

Otolaryngologists are familiar with the advantages of air calorics; in particular, the assessment of labyrinthine function in patients with tympanic membrane perforations, mastoid cavities and otitis externa. However, certain inconveniences have been pointed out such as the patient's discomfort due to acoustic stimulus produced by the air current, burning sensation of the external auditory canal, earache, and more variable caloric responses with air than with water.

We feel that a major problem is one of a reliable technique which includes constant air flow and temperature maintenance and a consistent stimulus placement.

INSTRUMENTATION

We use a commercially available air caloric stimulator.* The air temperature can be adjusted from 0 to 50 C. There are two preset positions for the bithermal test, 24 C and 50 C. The air can be adjusted from four to ten liters per minute in a float-ball flowmeter. The heating or cooling of the air is performed by a thermo-electric device located in the handpiece of the instrument, and the temperature is measured by means of a thermistor 106 mm from the delivery orifice.

The instrument can operate with a central air source. For mobility, however, it is preferable to use a pump powered by an electromagnetic vibrator which requires no lubrication and delivers a constant air flow.** An air filter is incorporated in the system at the point where the air hose connects to the instrument.

Instrument location can be important. Care should be taken not to place the air intake of the apparatus close to a

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*Manufactured by Instrumentation and Control Systems, Inc., Addison, IL.

**Reciproctor, Model AP-1. Instrumentation and Constrol Systems, Inc., Addison, IL.

From the Division of Otoneurology, William Beaumont Hospital, Royal Oak, Michigan.

Presented at the annual meeting of the American Audiology Society, Las Vegas, Nevada, October 5, 1976.

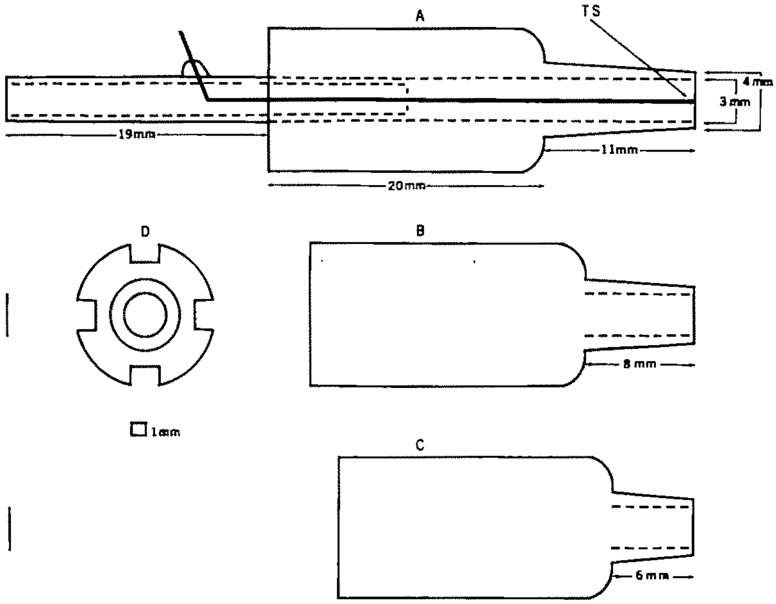

Fig. 1. Scale drawing of irrigating tips. (A) Probe for the majority of adult external ear canals. (B) Medium probe for narrow adult canals and younger individuals six to nine. (C) Small probe for children under six. (D) Cross-section (same for all probes) shows location of slots for proper back-flow. TS - Temperature sensor.

window or in any area where temperature variation may occur. It was noted that such environment interferes with stabilization of the cold stimulus. Temperature of the testing room is maintained at 21.1 C (±0.5 C).

PILOT STUDY

A pilot study was carried out with a few subjects to determine adequate stimulation parameters and establish an appropriate method of temperature measurement during air caloric stimulation. Simultaneous recordings of the temperature at the delivery orifice would allow objective comparison of the stimulus delivered in the aural canal from ear to ear and between patients.

A previously designed probe for water calorics was modified.* Four slots were made to allow adequate air back-flow (Fig. 1). The length of the portion of the probe that was inserted in the ear canal remained at 11 mm. The total length of the irrigating tip including the connecting tube is 50 mm. The inside diameter is 3 mm, and the outside diameter is 4 mm. Sixty second irrigation with this probe at an air flow of six liters per minute produced a nystagmus intensity (velocity of slow component) similar to our previous values for water irrigation. It was observed that the depth of the probe within the aural canal was a critical factor determining response. For example, if the tip was moved outwards 5 mm, the nystagmus intensity (slow component velocity) dropped about 30% for the warm stimulus and about 10% for the cold stimulus.

Temperature measurements were performed during actual caloric stimulation adding a second thermistor (520X)** placed inside of the irrigating probe flush with the delivery orifice (Fig. 1). This thermistor registered simultaneously the temperature on the recording paper of the electronystagmograph (Fig.

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*Made to our specifications by Mr. John VanGamen, Department of Medical Engineering, William Beaumont Hospital, Royal Oak, MI.

**Yellow Springs Instruments, Yellow Springs, OH.

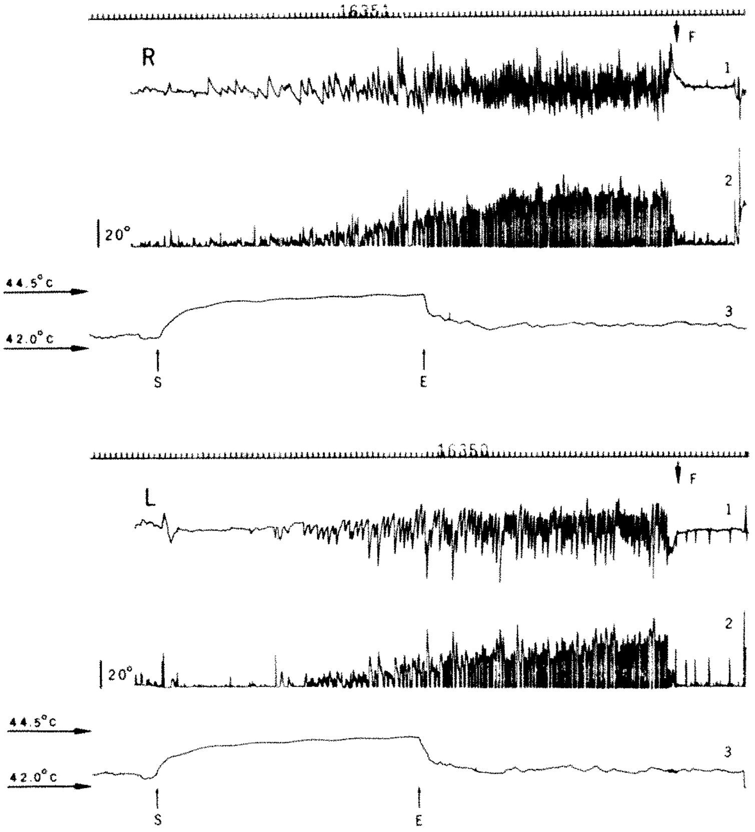

Fig. 2. Temperature measurements during warm caloric stimulation of right (R) and left (L) ears. (1) Eye nystagmic movement. (2) Nystagmus velocity (method of Henriksson). (3) Recording of air temperature, sensor position shown in Figure 1. S - Start of stimulus. E - End of stimulus. F - Optic fixation suppresses nystagmic response.

2) using a special coupler (9858).* For warm stimulation, the instrument was set at 50 C which yielded a mean temperature of 45 C at the delivery orifice within the ear canal at 60 seconds. The cold stimulus was set at 24 C which stabilized to a mean temperature of 27.4 C (N = 20, 40 ears).

The effective temperature of the aural canal upon the thermistor was measured by placing the "standard" probe in the canal in the testing position but without air running through it. The average temperature registered by the sensor flush with the delivery orifice was 35.4 C at 60 seconds (N = 10, 20 ears).

Variations in the external ear canal size and shape did not permit the use of the same probe in all ears. Accordingly, we designed medium and small size probes (Fig. 1) with the inside diameter of 3 mm. The portion that was inserted in the aural canal for the medium size is 8 mm and fits narrow ear canals and children aged 6 to 9 years. This measurement is 6 mm in the small size probe which is used in younger children. The distance from the delivery orifice to the end of the connecting tube remained at 50 mm using longer tubes.

Capps et al,[6] in their evaluation of air calorics, suggested a waiting period of three minutes between irrigations. To further investigate this suggestion, temperature measurements were made in an anesthetized cat which had bilateral

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*Beckman Instruments, Schiller Park, IL.

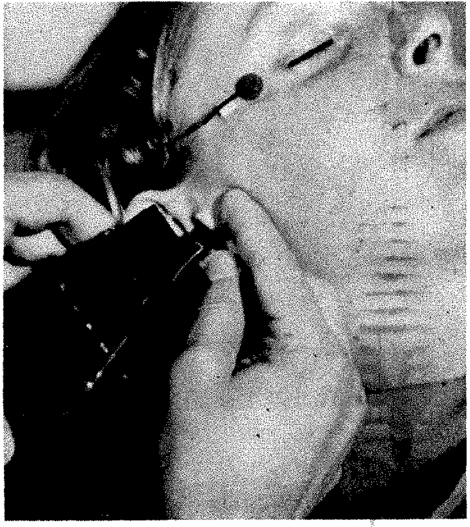

Fig. 3. Air stimulation of the right ear. Note the handpiece of the stimulator resting on the examining table. The examiner only guides it into position.

auriculectomies performed several months prior to this experiment. A thermistor (520X)* was placed in the middle ear through a burr hole in the posterior epitympanum with its tip lateral to the long process of the incus. Temperatures were observed to return to preirrigation values within three minutes for both hot and cold air stimulations. Thus, this tended to support the notion that a waiting period of three minutes would be adequate for air caloric testing.

TECHNIQUE

To perform the test, air flow was set at 6 liters per minute. The stimulation time was 60 seconds; and instrument settings of 50 C and 24 C were used.

The patient lay on a double dropleaf examining table with eyes closed in semidarkness. The cephalic end of the table was raised to bring the head of the patient 30° above horizontal. The upper portion of the helix of the ear was and should be aligned with the edge of the table to facilitate stable positioning of the stimulator's handpiece. For the right irrigation, the external ear was held with the thumb, index and middle fingers of the right hand. The handpiece of the stimulator was held with the left hand. The probe was then introduced into the external ear canal under direct visualization with the aid of a head lamp until the broad portion reached the concha. The handpiece rested on the examining table while the examiner merely guided it into position (Fig. 3). It was essential that the examiner brace himself with his arms on the table so that a comfortable position was maintained for a full 60 seconds without changing the probe position.

For the left irrigation, the external ear was held with the thumb, index and middle fingers of the left hand. The handpiece of the stimulator was held with the right hand. The probe was introduced into the external ear canal until the broad portion reached the concha in the same position as in the opposite ear. The examiner took care not to hold the irrigating tip with his fingers because the temperature of the air stream can be significantly modified, particularly the cold irrigation.

NORMAL STUDY

A normal study was carried out with the standard (11 mm) probe. Thirty volunteer subjects from the hospital staff were tested. They ranged in age from 20 to 57 years with a median age of 25.5 (2 male, 28 female). They had normal hearing and no history of otoneurological disorders. There were no subjects within the group who were particularly sensitive to motion.

A complete ENG battery was conducted using bitemporal leads. The direct eye movement was recorded and the velocity of eye movement was determined by the method of Henriksson.[7] For the purposes of this study only the findings due to caloric stimulation by air will be discussed.

The caloric stimulation was presented in the manner described above. Testing was performed with eyes closed in semidarkness. Hot left stimulation was presented first. During the poststimulatory caloric response, mathematical alerting was used, interjected with verbal questions to keep subjects well alerted.

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*Yellow Springs Instruments, Yellow Springs, OH.

A waiting period of a minimum of three minutes after termination of the poststimulatory caloric response was imposed before stimulating the right ear. Again there was the same waiting period before stimulating the left ear with cold stimulus. After the final rest period, the right ear was stimulated with cold stimulus (HL-HR-CL-CR).

Initially when performing the caloric test with water, the sequence suggested by Hallpike had been followed (CL-CR-HL-HR). Hart,[8] among others, later suggested that the hot caloric provides more reliable and valid data concerning the status of the labyrinth. The caloric order was, therefore, modified placing the hot stimulus first (HL-HR-CL-CR), and the same sequence was followed for air stimulations.

Measurements used for objective evaluation were the ten second average velocities of the slow component by electronic differentiation[7] taken at the period of maximum poststimulatory response. The ranges for hot stimulation were 10.2-43.2 °/second and for cold were 11-47.2 °/second. The means and standard deviations for each of the four air stimulations for the 30 normal subjects are presented in Table 1. The *t* tests shown (for correlated samples[9]) in the figure indicated no significant difference (.05 level) between the left and right stimulations for hot. The same finding was noted for cold stimulations as well. The actual *p* obtained is shown for information purposes only. The determined values of at least .50 or 50% further substantiate that the left and right responses from the respective stimuli are indeed quite close.

The mean velocities shown in Table 1 can be seen to be very similar for all conditions. Cold responses may be slightly less than those produced by warm stimulation. A correlated *t* test that compared grouped warm and cold responses showed no significant difference ($t = .9$, $p = .35$ or 35%). This was quite surprising, since no attempt had been made to equate warm and cold stimuli in this manner.

TABLE 1. AIR NORMAL STUDY

	Mean	*S.D.*	*t**	*p*
Hot left	21.9	8.3	0.7	.50
Hot right	21.8	7.7		
Cold left	21.4	8.5	0.6	.55
Cold right	20.3	7.1		
Jongkee's formulae				
Unilateral weakness	.65%	8.0% left down		
Directional preponderance	−. 9%	6.3% right nystagmus		

*t test for correlated samples.

Most investigators are familiar with Jongkee's formulae for vestibular assessment.[10] Each subject's responses were evaluated for vestibular weakness and directional preponderance. The mean percent and associated standard deviation are presented in Table 1. It can be seen that there was a very slight tendency for the left ear responses to be diminished. Also, there was a slight preponderance of the right nystagmic responses. Of interest here are the standard deviations which are quite comparable to those values calculated for normal water testing by Aschan et al,[11] Henriksson,[12] Preber,[13] Jongkees et al,[10] and Coats.[14] In fact, some of these investigators have shown a larger deviation for water irrigations. Using the clinically accepted two times the standard deviation, a 16% value for cutoff for unilateral diminution and a 12.6% value for directional preponderance was indicated. Findings greater than these values would suggest abnormal vestibular function. These cutoffs are dependent upon our technique and equipment. Ideally, each vestibular laboratory should make its own determination of normal values associated to any type of caloric testing. It is felt that this is even more important when dealing with air stimulation.

Since the air probe had been developed from the same probe used in water caloric testing, data was available from previous normal water testing for comparison. The sample size was

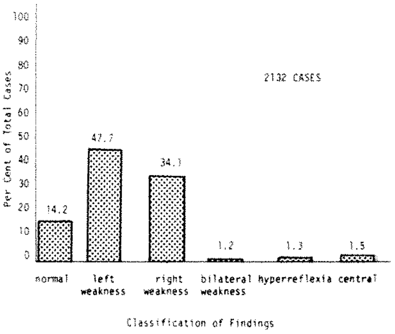

Fig. 4. Results of air caloric testing of 2132 patients.

slightly smaller (N=24), and the subjects were not the same used in the present study. Only general comparisons were made out of interest. Warm water (44 C) and cold water (30 C) irrigations of 30 seconds with five minute waiting periods presented responses that were slightly greater than for air. Again, mean slow phase velocity of the respective responses was used for response evaluation. Warm water stimulation produced responses one-third greater than did air stimulation. Cold water stimulation was only one-fifth greater. Thus, water did give slightly stronger responses than the air stimulation as administered in this investigation. This was more evident for the warm stimulus.

CLINICAL CASES

At this time 2132 consecutive cases have been tested with identical equipment.* The median age was 50 years. The use of the smaller probe allowed testing of a 17-month-old patient, and the oldest patient tested was 84 years. Fifty-eight percent were female.

Figure 4 shows a classification of findings. Percentage of normals refers to patients in which the ENG battery did not show vestibular abnormalities. Complete work-up revealed systemic disorders or other otologic disease without involvement of the vestibular system. Percentage of hyperreflexia refers to patients with peripheral vestibular disorders which were not included in the percentage of central cases. There was excellent tolerance of the air irrigations by the patients. For certain motion sensitive individuals, stimulus time had been reduced to 45 seconds and observed responses have been informative.

During clinical administration, it was observed that for appropriate air stimulation the external ear canal must be meticulously cleaned prior to testing. Partial blockage of the irrigating probe by cerumen interferes with the air flow as well as the sensor that monitors temperature at the delivery orifice. When impacted cerumen must be removed by irrigation with water, air stimulation characteristics are drastically altered due to evaporation of the remaining moisture in the aural canal. This has a greater effect with warm stimulation. Even a complete reversal of expected nystagmic response has been observed. One remedy for this problem, in lieu of having the patient return at another time, is to perform a warm air stimulation for 60 seconds in each ear to dry the canal. The actual testing is then performed presenting the cold air first. Caution should also be used for evaluating responses when the external meatus is damp for other reasons.

DISCUSSION

The investigations of Proctor et al[5] showed clearly how important was the design and construction of the irrigating probe. They concluded that critical variations of the irrigating temperature originate within the tip itself. In a recent report, Coats et al[15] also determined that the point in the irrigating tip at which the temperature was measured is critical. In addition, they found significant temperature variations according to the depth of the irrigating tip within the external auditory canal.

In the present study, when the "standard" probe is used the portion of the tip which is introduced into the external ear canal is 11 mm. This measurement remains quite close because the broad portion of the probe can be consistently placed from ear to ear at the level of the concha. In the adult, the average length of the external ear canal is 25 mm measured from the bottom of the concha and 40 mm measured from the tragus.[16] Coats et al[15] reported that the depth of their irrigating tip was about 18 mm from the outer surface of the tragus, therefore, they stimulated approximately 22 mm from the tympanic membrane. With the "standard" probe, stimulation occurs at 14 mm from the tympanic membrane which makes a difference of about 8 mm. We feel this is significant because Coats et al,[15] in their excellent study, demonstrated that when the tip was moved outward only 7 mm the warm air response intensity dropped by about 40%. This may explain why a nystagmus of sufficient amplitude and intensity was obtained with an air flow of only 6 liters per minute rather than Coats' 13 liters per minute. Depth of the irrigating tip within the external auditory canal during air stimulation has not been reported by other authors.

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*There were 380 cases examined at the Lakeshore Ear, Nose and Throat Center, Harper Woods, Michigan.

Capps et al[6] had reported that bithermal air stimuli of 24 C and 50 C yielded nystagmus of comparable intensity to those produced by 30 C and 44 C water. It is important to note that 24 C and 50 C air are the preset temperatures of the apparatus. It has been shown that these are not the irrigating temperatures as measured in the delivery orifice. The temperature as measured at the tympanic membrane would be different as well.

The temperature sensor in the delivery orifice is strongly influenced by outside temperature within the ear canal. Thus, this sensor reads a value between true air stream temperature within the nozzle and the temperature of air within the aural canal. It is felt that this reading represents a reliable estimation of the true irrigating temperature as close as possible to the eardrum. The thermistor in the delivery orifice should not substitute the thermistor in the handpiece of the stimulator. Each one has its own function; the latter controls a constant temperature in the system and the former only monitors the temperature of the irrigating stream. When the temperature is recorded as described above on the ENG, the course of stimulation can be observed and compared between ears. Therefore, an objective measure is available that can indicate the consistency of stimulation.

The mean velocities reported showed a tendency for the warm stimulus to produce a greater caloric response. However, if the mean irrigating temperatures (45 C and 27.4 C) were compared to body temperature (37 C), it would appear that the hot stimulus created a lesser difference (8.0 C) than the cold (9.6 C). This inconsistency may be resolved by considering the temperature measured within the aural canal. When the average ear canal tip temperature (35.4 C) was compared to the mean stimulating tip temperatures, the hot stimulus now shows a greater difference (9.6 C) than the cold (8.0 C). This finding is in more agreement with the observed responses. Thus, the temperature of the ear canal should be considered when determining the effective air caloric stimulation.

Variability of repeated air testing is certainly an important factor as shown by the recent Coats et al[15] publication. Repeated testing has been performed for evaluation of clinical patients for drug ototoxic effects (e.g., gentamicin). Remarkable correspondence has been observed in responses for as many as three testing sessions in eight weeks.

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FINE-NEEDLE BIOPSY OF THE THYROID GLAND

A CYTOHISTOLOGICAL COMPARISON IN CASES OF GOITER

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SUMMARY — At the ENT Clinic of the Regional Hospital in Örebro, cytological investigation of fine-needle biopsy specimens has been carried out to a steadily increasing extent for more than ten years as a complement to clinical methods of investigation and laboratory tests in cases of goiter. Evaluated here are the method's diagnostic accuracy and its value in investigatory work. The material consists of 303 patients with goiter who were operated from 1964 to 1971 following fine-needle biopsy. Cases where biopsy only was undertaken are not included. Assessable cytological material was obtained in 284 cases (94%). Although not less than 15 doctors carried out the fine-needle biopsies there was approximately a 93% agreement between the cytological and histological diagnoses. In 15 of 28 cases of thyroid carcinoma it was possible to make a definite diagnosis preoperatively, while in 12 of the remaining cases atypia suspected of malignancy was found. The possibility of being able to demonstrate or suspect a carcinoma preoperatively is of great importance for the surgeon, as a more extensive intervention can be planned in advance and the patient informed before the operation.

Cytological investigation of fine-needle biopsy material has been carried out to a steadily increasing extent at the Regional Hospital, Örebro, for more than ten years as a complement to clinical methods of investigation and laboratory tests in cases of goiter. The investigation presented here was carried out to evaluate the diagnostic accuracy of the method with our routine. The fine-needle biopsies were not carried out by a cytologist but by approximately 15 doctors at the ENT Clinic. The primary cytological assessment has with few exceptions been carried out by a small number of cytopathologists at the hospital's Department of Pathology and rechecking has been wholly carried out there. This procedure distinguishes the investigation from most others where both the fine-needle biopsies and assessments are carried out by only a few doctors and perhaps even the same doctor. From our point of view the most interesting group is thyroid carcinoma, where we aim for a preoperative diagnosis in case further investigation should be required, and in order to be able to plan a more extensive intervention, and also to have the possibility of informing the patient about it in advance.

METHODS AND MATERIALS

The material is derived from all of the 408 patients subjected to strumectomy at the ENT Clinic during the years 1964-1971. All specimens were examined histologically. Cases where only biopsy was carried out are not included in the material, this only including patients with atoxic goiter as cases of thyrotoxicosis were treated by the Surgical Clinic of the hospital.

Preoperative fine-needle biopsy was carried out in 303 of these strumectomy cases. During the early years from 1964 such biopsies were seldom done. As the cytologists' experience increased, so confidence grew for this kind of investigation and during the last years of the investigation almost all patients were subjected to fine-needle biopsy preoperatively.

The technique described by Franzén[1] has been used. During the latter years of the investigation the special aspiration syringe was replaced by a disposable syringe with a removable handle as described by Hollender and Persson.[2] The aspiration biopsy has been carried out on the basis of palpation observations and/or ^{131}I scintigram.

The material was divided cytologically and histologically into four groups: benign, atypia (adenoma), thyroiditis, and malignancy. Under the cytologic heading "atypia (adenoma)"

From the Department of Pathology and the ENT Clinic of the Regional Hospital, Örebro, Sweden.

TABLE 1. CYTOHISTOLOGICAL COMPARISON IN 284 CASES OF OPERATED GOITER

	Benign	*Atypia (Adenoma)*	*Thyroiditis*	*Malignant*	*Total*
Histology					
Benign	169	9	—	—	178
Adenoma	7	52	—	—	59
Thyroiditis	—	3	16	—	19
Malignant	1	12	—	15	28

have been gathered those cases, usually with a rich yield of cells, exhibiting more or less aberrant cytological details but without convincing criteria of malignancy or thyroiditis. Most of these were reported as probable adenomas and extirpation was suggested by the cytologist. By the histological heading "adenoma" is meant adenomas with or without a varying degree of cellular atypia but without signs of carcinoma in the form of invasion of vessels, penetration of the tumor capsule or signs of metastasis.

The cytohistological comparison was carried out on the basis of the original cytological and histological reports. In a small number of cases, especially during the earlier part of the investigation period, the formulation of the reports was not uniform and in such cases the cytological specimens were rechecked by one of us without knowledge of the histological diagnosis. The cytological investigations were made preoperatively and thus without knowledge of the ultimate histological diagnosis. Most of the cytological investigations were carried out by one of us (LBS) while most of the histological assessments were done by another senior pathologist. The rest of the investigations were made by a few other pathologists. A transfer from one of the four histological groups of diagnoses to another, influenced perhaps by a diverging cytological diagnosis, is considered practically impossible. The histological diagnosis based on investigations made on the entire operative specimen is therefore considered as final.

RESULTS

Assessable material was obtained in 284 cases of fine-needle biopsy (94%). The comparison between cytological and histological findings is shown in Table 1. Of the 178 cases with a benign histological picture, usually nodular goiter, 9 cases showed slight cytological atypia. In 59 cases there was adenoma of the microfollicular or trabecular type. In seven of these cases only normal follicular epithelial cells were discovered cytologically and the cases referred to the benign group. Of the 19 thyroiditis cases, 16 were diagnosed preoperatively while the remaining 3 were classed as "atypia." In the thyroid carcinoma group, a positive cytological diagnosis was made in 15 of 28 cases while malignancy was suspected in 12 cases and therefore shown under the heading "atypia (adenoma)."

There was complete agreement between histologic and cytologic diagnosis in approximately 93% of the cases. The diagnostic accuracy within the different diagnosis groups is shown in Table 2.

In the 19 cases where a representative cytological material was not obtained, the histological diagnoses, including carcinoma, were grouped as in the material investigated cytologically.

TABLE 2. AGREEMENT BETWEEN CYTOLOGICAL AND HISTOLOGICAL DIAGNOSES

Diagnostic Groups	*No. of Cases*	*%*
Benign (mainly nodular goiter)	169/178	95
Adenoma	52/59	88
Thyroiditis	16/19	84
Carcinoma (including cytological suspicion)	27/28	96
Total	264/284	93%

The fine-needle punctures have been practically painless and there have been no complications.

DISCUSSION

Of the 303 cases where fine-needle biopsy was carried out preoperatively, assessable material was obtained in 284 cases (94%). Einhorn and Franzen[3] in 1962 showed assessable cytological material in 523 cases (98%) of 535. It is theoretically possible to obtain a 100% result if the same doctor carries out both the biopsy and the cytological assessment, as he is better able to assess the material in connection with the aspiration and to repeat the puncture until the return obtained is satisfactory. This demands, however, a cytologist with a clinical bent or a clinician interested in cytology. Because of organizational and personnel problems such a routine is always difficult to achieve. If instead only a few doctors do the biopsies a better result than 94% would probably be obtained. The advantage of our system is that the doctor carrying out the biopsy is the one who best knows the patient's medical history and is able in addition to follow the local status and register any changes that may occur. In order to obtain a good result it is essential that the clinician is well-acquainted with the technique. It is emphasized that requests for cytological investigation must be detailed and that it is important to state in the request whether the thyroid gland itself has been punctured or a lump in the neck is independent of the thyroid.

In the group entitled benign histologically, usually embracing cases of nodular goiter, there were nine cases of slight cytological atypia. A histological rechecking of the operation specimens of these goiters showed areas with proliferative epithelium but with no suspicion of tumor and it is considered that these findings can explain this slight cytological atypia.

In the histological adenoma group totaling 59 cases there are 7 cases with only benign cells cytologically. A rechecking of the specimens for these seven revealed the adenomas to be of the follicular type, rather colloid rich but without atypia and, in any case, the cytological material obtained was very sparse. In the remaining 52 cases cytologically cell rich smears were obtained. These were in most cases considered to represent an adenoma but as they were more or less atypical in the wider sense of the word they were always recommended for operation by the cytologist.

As was pointed out by Löwhagen and Sprenger,[4] and others too, it is in fact not possible to distinguish cytologically between a highly-differentiated follicular thyroid carcinoma and cell rich adenoma as the diagnosis in these cases depends on the demonstration of capsule penetration, vessel invasion or the appearance of metastases.

Of the 19 thyroiditis cases 3 were cytologically classified as atypia only and a reexamination showed this to depend on a much too scanty cytological material poor in lymphoid components. In these cases the patients were operated on because of clinically suspected malignancy. As has been maintained by Persson[5] and others it is not possible in lymphoid thyroiditis to exclude definitely the possibility of a simultaneous malignant process and he considers that if the goiter does not respond to thyroxine treatment after 2-3 months, then the patient should be operated on. Welch and Hellwig[6] state a malignancy risk of 10-12% in their material in cases of Hashimoto's disease. Crile and Hazard,[7] on the contrary, did not find in their series a single case of carcinoma in this type of thyroiditis.

In the group recommended for operation because of the cytological findings, 27 of the 28 carcinoma patients (97%) are found. As was said earlier, 15 were considered to be obviously malignant while 12 cases were assessed as atypia. In one case the cytologist misinterpreted the cytological findings. However, the investigation of this case took place just as the cytological activities had started so that the misinterpretation must be ascribed mainly to the cytologist's lack of experience, as the preparation is excellent and on reexamination permits the diagnosis quite clearly.

Einhorn and Franzén[3] showed in 52 cases of preoperative fine-needle biopsy of the thyroid, later surgically treated for thyroid carcinoma, a malignant cytology in 35 cases and suspected malignancy in 13 cases. In fine-needle biopsy of suspected metastases, later verified, the cytological investigation showed malignant cells in 30 of 32 cases and suspected malignancy in 1 case. The discrepancy in the result probably depends on the fact that it is easier to obtain a representative return from a metastasis than from the thyroid gland itself, and also that it is easier to reach the conclusion that malignancy is present when atypical thyroid cells are discovered in a lymph gland puncture than in a material from the thyroid gland, especially if it is a case of a highly differentiated carcinoma.

The diagnosis of carcinoma of the thyroid gland should as far as possible be made preoperatively, making it possible to carry out further investigations if necessary, and plan the operation, and also to inform the patient beforehand that it may be necessary to carry out a more extensive intervention, perhaps in conjunction with the transplantation of parathyroid tissue to musculature away from the neck region.[8] Very great difficulties arise in identifying the parathyroid gland in a reoperation, should this become necessary.

The reasons stated above, apart from any other considerations, strongly indicate preoperative fine-needle biopsy of the thyroid gland with cytological investigation of the specimen.

It is considered, usually correctly, that the result of a fine-needle biopsy is best if the cytologist himself obtains the material.[9] In our opinion the investigation presented here shows that very good diagnostic results can be obtained even when the punctures are carried out by a number of clinicians. A condition, however, has been the training in palpation, puncture and investigational procedure that the ENT clinicians at Örebro have to go through before they carry out punctures independently. The intimate daily contact between the clinically active doctors and the Regional Hospital's cytologists and pathologists has most certainly been of great value for the good results obtained.

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SAFE INSERTION OF TRACHEAL T-TUBES

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SUMMARY — A modified technique for the insertion of silicone tracheal T-tubes is described and discussed. This modification reduces the danger of apneic intervals during the procedure.

The silicone tracheal T-tube was described by Montgomery in 1965.[1] It was designed for the management of tracheal stenosis, either as a definitive measure or as support for the reconstructed trachea. The essential value of this T-shaped silicone prosthesis is in maintenance of a patent airway while the tracheal wall is supported and reshaped.

Insertion of the T-tube is facilitated by its flexibility and design, and the technique was clearly described by Montgomery.[2,3] This standard technique has been found suitable and adequate for routine cases, i.e., primarily in changing or inserting tubes when the tracheal lumen is established and unobstructed.

During the past few years we have used silicone T-tubes on 14 patients and have gathered considerable experience in their management. While in general the routine technique for insertion and changing of the tubes proved adequate and safe, there were, however, exceptions. We found that inexperience and lack of confidence on the part of the surgeon occasionally prolonged the procedure causing extended and dangerous periods of airway obstruction.

Frequently we experienced twisting or kinking of the tube during its insertion, and occasionally found that the upper limb of the intraluminal portion refused to snap into position. The latter problem was encountered mostly with narrow tracheostomies, stenosis at or above the tracheal fenestra, and in subglottic stenosis. Furthermore, on occasions the tube failed to pass through the stenosed section despite adequate preliminary bougienage. In these circumstances even traction via the endoscope may prove insufficient to complete the maneuver quickly.

During these sometimes frustrating manipulations the patient suffers prolonged apnea, causing anxiety and distress to both the surgeon and the anesthetist. We therefore decided to modify the technique as follows: Prior to the insertion of the T-tube, a well-lubricated infant-size endotracheal tube was passed through the lateral limb of the T into the lower limb. At its proximal end the endotracheal tube was fitted with a standard anesthetic connector (Figs. 1, 2). It was essential that the endotracheal tube would in no way disturb the insertion of the T-tube, but would, at the same time serve, not only as a "non-kinkable" introducer, but would also allow adequate and constant ventilation of the patient during the T-tube insertion procedure. Thus when delays or difficulties were experienced the anesthetist was able to maintain adequate oxygenation by ventilating the patient intermittently, with 100% O_2 under pressure because of the narrow internal diameter of the endotracheal tube used. Having thus obviated the development of hypoxia during the apneic periods,

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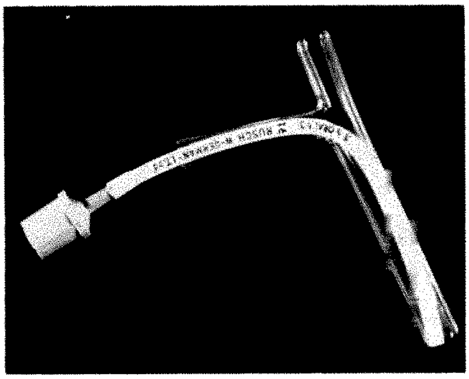

Fig. 1. The silicone tracheal T-tube seen with an endotracheal tube inserted, serving as an introducer and antikinking measure. The anesthetic adaptor is in position.

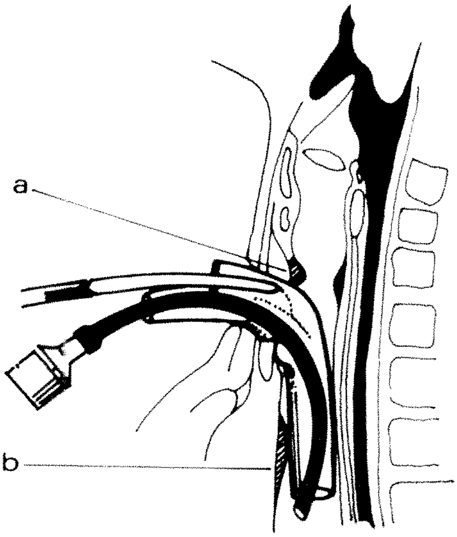

Fig. 2. Technique for insertion of the silicone tracheal T-tube with the endotracheal tube acting as both airway and introducer. a, b) Stenotic areas in the trachea.

the surgeon gained valuable time in the manipulation of the T-tube into position, by whatever means he may have found necessary.

We have found this modified technique to be an extremely helpful adjuvant to the basic original instructions, and invaluable in difficult cases. It is especially helpful in those circumstances when the surgeon feels he may be lacking in either the ability or experience to perform the procedure with the dexterity or speed which it demands.

Since adopting this variation we have found insertion of tracheal T-tubes to be not only trouble-free but also devoid of tension and anxiety.

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ACTINOMYCOSIS: MASQUERADER IN THE HEAD AND NECK

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SUMMARY — The diagnosis of cervicofacial actinomycosis is usually not simple, but may be essential for adequate treatment. Cases seen in a Head and Neck Service illustrate some of the many guises under which actinomycosis may be concealed, and a review of recent literature confirms its propensity to be a masquerader. A combination of techniques is necessary to diagnose, and both surgical and medical approaches are needed to treat this often distressingly persistent affliction.

The problem of actinomycosis as a cervicofacial disease and as a more generalized infection has been recognized since the late 1800s. Despite the efforts of Waksman[1] and the numerous researchers who preceded him in characterizing the offending organism, the disease is at best a distressing and disabling and at worst a life-threatening clinical problem. Actinomycosis is caused by organisms ubiquitous and yet fastidious; it is susceptible to the more familiar antibiotics, yet stubbornly persistent in the face of less than adequate therapy; it is infrequent enough to be readily overlooked in diagnosis, yet occurs in all parts of the rural and urban world; it is possessed of definable biological characteristics, yet chameleon in its locations and presentations. Actinomycosis is truly a masquerader and still a diagnostic and therapeutic challenge.

This study was prompted by the recent presentation of several cases of cervicofacial actinomycosis to the Head and Neck Service of the Columbia-Presbyterian Medical Center, Department of Otolaryngology, which reemphasized some of the problems encountered in dealing with this disease. A review of our institutional experience over the preceding 20 years, as well as that presented in the recent literature, supported certain concepts in diagnosis and management of actinomycosis of the head and neck and called others into question.

The inpatient records of Columbia-Presbyterian Medical Center were screened for patients with a diagnosis of actinomycosis of the head and neck region for a period of 20 years, 1955-1975. Surgical pathology records were cross checked. Microbiology, unfortunately, had no system of retrieval of cases by disease, except for certain infections with public health implications. In addition were included some patients seen in the private practice of the senior author as well as one seen in the outpatient clinic of this institution. Patient data is summarized in Table 1.

SUMMARY OF FINDINGS

Sites of Involvement. Varied sites in the head and neck were involved, some of which are illustrated in Figures 1-3. Three originated in the lower jaw, one of which eventually caused a neck abscess. Four presented as masses in the submandibular area. Three appeared over the parotid area, one accompanied by parotid duct discharge. Three presented with masses in the neck, one in an area of prior carcinoma. Two of the patients, one of which developed intrahepatic actinomycosis (Case 8) had cysts and sinuses of the facial skin.

Diagnostic Efforts. Most of the patients presented diagnostic problems.

From The Presbyterian Hospital, Columbia-Presbyterian Medical Center, New York, New York.

TABLE 1. GENERAL DATA

Number of cases	15
Period covered	1957-75
Age range	
0-20	0
20-40	5
40-60	8
60+	2
Sex	
Male	11
Female	4

Delay in diagnosis ranged from two days to three years, though the majority fell within the range of two weeks to a year (Table 2). In the majority of cases, several inadequate courses of antibiotics were given before the patient came to surgical excision of the infected tissue, with final diagnosis made by surgical pathology. Seven of the patients had the diagnosis confirmed only by histopathology, and four by culture alone. In two cases, both culture and biopsy were positive. Two diagnoses were made on smear, one patient having had negative cultures and biopsy. In this case "sulfur granules" were finally noted in a recurrent discharge and culture confirmed actinomycosis (Case 9).

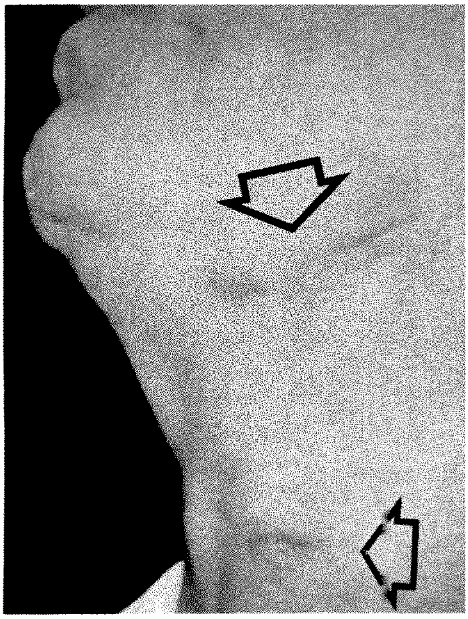

Fig. 1. Multiple sinuses of neck skin from actinomycosis.

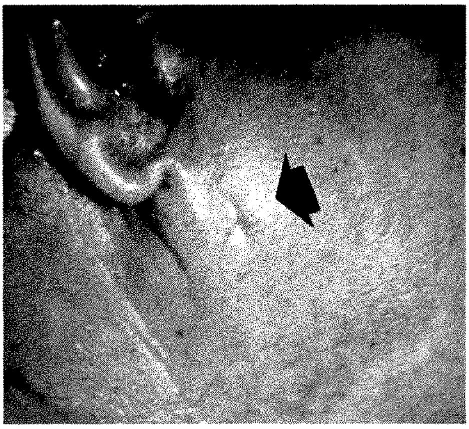

Fig. 2. Draining parotid abscess with actinomycosis.

The delay in diagnosis was prolonged in most of the cases by failure to consider actinomycosis as a possibility. Initial diagnosis varied, and there were only three cases in which actinomycosis was mentioned in the original differential diagnosis, once as a primary and twice as an alternative diagnosis (Table 3). There were also repeated drainage procedures which failed to establish the

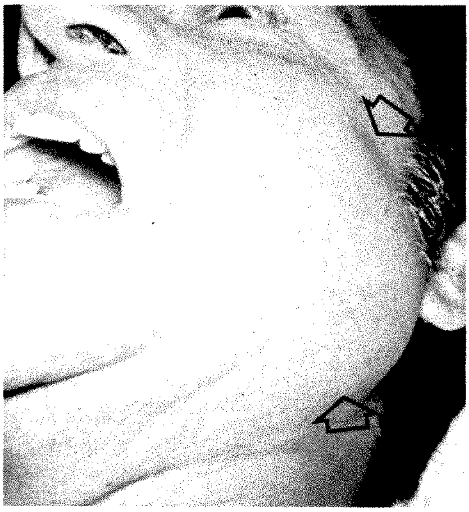

Fig. 3. Actinomycotic abscess of parotidomasseteric space causing trismus and swelling.

TABLE 2. DELAY FROM PRESENTATION TO FINAL DIAGNOSIS

1-7 days	1
1-4 weeks	5
1-6 months	5
6-12 months	1
1-3 years	3

diagnosis and repeated antibiotic courses inadequate to eradicate the actually existing disease (Table 4).

Therapeutic Measures. Among the antibiotics used ineffectively prior to diagnosis in ten cases were tetracyclines, penicillins, sulfa, chloramphenicol, lincomycin, and clindamycin. Many of these were also used for definitive therapy, as summarized in Table 5. Success at that point may be attributable to prolongation of the course and concomitant surgical intervention. All the patients had surgery in the form of at least incision and drainage and/or biopsy, and seven had a major resection of the infected tissue at formal operation. Only one of the patients who underwent resection is recorded as having failed to be cured thereby (Case 9), whereas eight patients who had incision and drainage procedures with or without final gross resections had multiple such procedures performed before relief was finally obtained.

TABLE 3. INITIAL IMPRESSIONS

	Primary	*Secondary*
Abscess	5	1
Sialadenitis	3	
Neoplasm, primary	3	
Neoplasm, recurrent	1	
Granulomatous disease		2
Lymphadenitis	2	
Actinomycosis	1	2
Infected branchial cleft cyst		1

Follow-ups were not as adequate as desirable, a typical disadvantage of a retrospective study such as this. Some of the patients with short recorded follow-up had persisted with their physician through many unsuccessful maneuvers, and it is likely that the lack of further record signalled final success. Table 6 summarizes the results of therapy. The one death is that in Case 8.

TABLE 4. INEFFECTIVE TREATMENTS PRIOR TO DIAGNOSIS OF ACTINOMYCOSIS

	No. of Patients Undergoing Treatments	
Number of Treatments	*Surgical Procedures**	*Antibiotic Courses*
0	7	5
1	6	3
2	1	4
3	1	2
4		
5		1

*Not including the procedure which led to establishing the final diagnosis.

CASE REPORTS

The case numbers are assigned as they appeared chronologically in our series of 15. Not all cases are reported.

Case 1. A 50-year-old male began to have pain and swelling in the left lower jaw in May 1957 and had two teeth extracted in June after dental x-rays by a private dentist. He continued to have swelling and pain and a private physician incised and drained the area. No culture report was noted. He was put on Achromycin® with some relief, but the symptoms soon recurred, and he was given another course of the drug. The symptoms recurred again, and he presented to the Medical Clinic.

He was referred to Dental Clinic where actinomycosis, tuberculosis, and osteomyelitis were considered. On December 11 he was presented to Combined Tumor Conference. Sinus and mandible x-rays were ordered and were negative for bony destruction. On December 27, culture and biopsy were taken. The culture was positive for actinomycosis. No mention was made of further treatment until admission in June 1958 for excision of the mass over his jaw with the same symptoms. The surgery was cancelled for reasons unexplained, and he was treated with potassium iodide drops and Achromycin®. He was well until March 1960 when he had a recurrent fistula, drainage, and pain. He was treated for a month with Terramycin®, the lesion cleared, and he remained symptom-free until September 1962, the last recorded visit.

Case 2. A 44-year-old male was admitted to the Head and Neck Service in February 1958

TABLE 5. ANTIBIOTIC THERAPY OF ACTINOMYCOSIS PATIENTS

Antibiotic	*Route*	*Duration*	*Cases*
Tetracycline	P.O.	6 weeks	4
	P.O.	Unspecified	3
Bicillin	I.M.	Weekly X 2 months, then biweekly X 6 months	1
Penicillin	P.O.	4 months	1
	P.O.	2 months	1
Sulfadiazene	P.O.	Unspecified	1
Clindamycin	P.O.	Unspecified	1
Lincomycin Tetracycline	P.O.	Unspecified	1
Tetracycline Lincomycin Clindamycin	P.O. I.V. P.O.	Day 1-14 Day 11-18 Day 18-25	1
Unknown	—	—	1

with a history of pain and swelling in the right submandibular gland region accompanied by fever beginning in September 1957. He was treated at that time with Albamycin® for a week with reduction in the symptoms, but had a flareup in December. He was again put on Albamycin® for a recurrence in January 1958 with no relief. Chloromycetin® and a sulfonamide were started, and he had an incomplete remission. The lesion continued to fluctuate in size and tenderness, and another week's course of Terramycin® and sulfonamide in early February was unsuccessful. There was a strong family history of tuberculosis and he was admitted for the resection of his right submandibular gland and accessory nodes with suspicion of carcinoma or granulomatous disease.

TABLE 6. RESULTS OF ACTINOMYCOSIS THERAPY

	Cases
Follow-up unrecorded	3
Asymptomatic	
2-8 week follow-up	4
2-6 month follow-up	3
2-5 year follow-up	3
Recurrent drainage after two years, treated with tetracycline one month, asymptomatic for three-year follow-up	1
Death	1

The pathological specimen demonstrated actinomycosis. Culture reports were not recorded. He was placed on Achromycin® postoperatively and the lesion appeared to resolve fully before discharge a week after surgery. Total duration of antibiotic treatment was not mentioned.

Case 8. A 57-year-old female presented to the Plastic Surgery Clinic in October 1969 with cysts of the face. The possibility of actinomycosis was raised. No mention was made of the duration of symptoms. Incision and drainage were carried out and a biopsy was submitted. Culture was negative, but actinomycosis was seen by surgical pathology. She was put on intramuscular benzathine penicillin G from November 7 to December 19, and the lesions slowly regressed. She then continued on bi-weekly injections until April 3, 1970, when it was noted that the lesions were nearly resolved. She finally was taken off the injections on June 5 and was discharged.

On November 8, 1972, she was admitted to the Medical Service for "lifelessness" and a temperature of 38.9 C. On the second day of admission, a chest x-ray showed a right middle lobe infiltrate, and she was started on oral cephalexin. On the third day she had a bronchoscopy negative for mass lesion, and on the fourth day diabetes was diagnosed. She manifested right upper quadrant tenderness on the sixth day and had a hypotensive episode on the seventh. A liver scan was done on the tenth admission day which demonstrated an intrahepatic mass lesion. Later the same day she suffered a massive pulmonary embolus and died. Autopsy findings included an actinomycotic abscess of the liver.

Case 9. A 50-year-old male was admitted to the Head and Neck Service in February 1971 after several courses of antibiotics given elsewhere for a left submandibular mass following treatment of an abscess of a left lower tooth ten months previously. He underwent surgical excision of a sinus tract and fistulas in this area (Fig. 1), and a catheter was inserted for three days of irrigation with a neomycinbacitracin solution.

Culture report was staphylococcus coagulase negative, and histopathology demonstrated an inflamed sinus tract. He was put on a regimen of erythromycin 500 mg orally every six hours for two weeks. Drainage recurred, and on a subsequent office visit in April 1971 an incision and drainage was performed. This demonstrated "sulfur granules," which were confirmed by the microbiology laboratory as actinomycosis. The lesion resolved on four months of oral penicillin therapy, 250 mg four times daily.

Case 11. A 40-year-old male presented with a three-year history of intermittent swelling of the right cheek with purulent parotid duct drainage. He had external incision and drainage twice by other physicians and had some discharge from this region (Fig. 2). When cultures showed pseudomonas, he was admitted for insertion of catheters into the gland for gentamicin irrigation and a course of intramuscular gentamicin. The problem seemed to resolve on ten days of this therapy, and he was discharged. Two weeks later he returned with reinfection and was placed on carbenicillin. Cultures sent to the mycology lab were highly suggestive of actinomycosis, though a pathology specimen showed only chronic sialadenitis. He was discharged on a tetracycline antibiotic and readmitted two weeks later for lateral lobe parotidectomy. Preoperative cultures were negative, and the pathology specimen revealed chronic sialadenitis. He was discharged on a course of tetracycline and no further problems were recorded.

Case 12. In July 1972 a 58-year-old male was admitted for exploration of a swelling in the left premasseteric space. In August 1970, after a mandibular molar extraction, he had developed swelling of the jaw and was treated for abscess with antibiotics. In April 1971 he again developed a mass with pain and trismus (Fig. 3), and this again resolved with antibiotics after incision and drainage. The symptoms recurred in September 1971, and antibiotics enabled increased range of motion, but the mass persisted. His admitting diagnosis was actinomycosis, with the possibility of carcinoma.

The exploration of the left premasseteric space yielded no pus, but thickened and fibrotic muscle and soft tissue. Pathology was nonspecific, but culture demonstrated actinomyces and a range of bacteria. He had a catheter placed for irrigation with a neomycinbacitracin solution. He was given tetracycline on postoperative days 1-15, lincomycin intravenously from days 11-18, and clindamycin orally from days 18-25. No further recurrence was noted.

Case 13. A 50-year-old male presented in May 1974 to the emergency service with three days of swelling, tenderness and heat in the right neck. He was given penicillin, but the lesion persisted, and he was admitted and placed on oxacillin, which was changed to cephalothin a day later after an abscess in the neck was drained under local anesthesia and the discharge cultured. No organisms were demonstrated, and he was discharged on oral cephalexin.

In August 1974 he returned relating a recurrence of the mass in June which had drained spontaneously, then recurred again. The area was drained and packed. On follow-up a week later the question of a recurrently infected branchial cleft cyst was raised, and he was admitted for excision of the neck mass. The pathology specimen consisted of actinomycotic abscesses in cervical lymph nodes. No cultures were sent. He was discharged on six weeks of tetracycline, after which there was no recurrence, and he was discharged from follow-up.

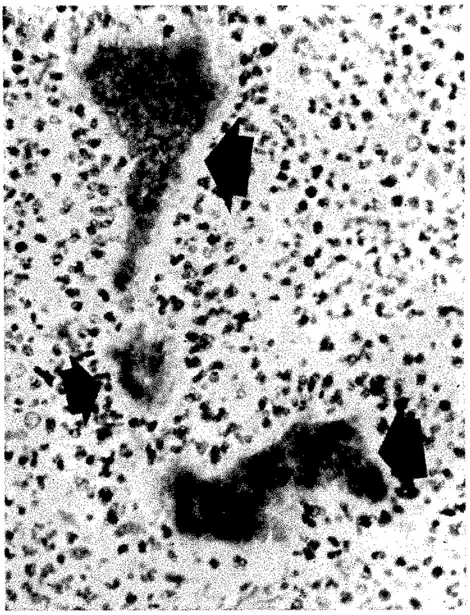

Fig. 4. Actinomycosis in granulation tissue from abscess. (PAS X40)

Case 15. A 65-year-old male was seen in the Head and Neck Clinic in August 1975 with a nodule in the left upper neck. He had had a left partial glossectomy, left hemimandibulectomy and a left radical neck dissection in 1969 for a squamous cell carcinoma of the tongue, with postoperative radiotherapy. He also had had a course of ampicillin in December 1972 for an infection in the operated area which seemed to resolve completely.

The nodule seen was suspected of being recurrent carcinoma and a biopsy was taken. Surgical pathology reported not carcinoma, but rather actinomycosis in the tissue submitted (Fig. 4). Oral penicillin, 500 mg four times daily for two months, was given and the lesion resolved. There was no recurrence on a follow-up three months after completion of therapy.

DISCUSSION

There has been much written on actinomycosis. Waksman[1] summarizes the biology of these organisms, a study which comprised much of this Nobel laureate's life work. Bronner and Bronner[2] give over 500 references and reproduce dozens of reports from the world literature up to 1970 in their book on the clinical aspects of actinomycosis. We make reference to some 20 other articles published since their book appeared.[3-22]

Actinomyces israelii, the human infective agent, is a rather delicate organism, and more difficult to cultivate than the aerobic members of the genus that grow in a natural state in soil and on organic residues. It is primarily anaerobic and grows best in the absence of oxygen or with a limited supply. The organisms are frequently referred to as fungi, but more recent evidence points to a close relation to true bacteria, based on cell wall and protoplasmic similarities, reaction with phages, and antibiotic sensitivity. They are somewhat fastidious and require a carefully balanced diet for growth.[1,2]

Since actinomycosis may be difficult to isolate, and since it tends to masquerade as a more familiar infective or neoplastic process, there is frequently a prolonged course with abortive attempts at cure with inadequate regimens of antibiotics. As Everts[6] comments:

> Cervicofacial actinomycosis is often referred to the otolaryngologist as a diagnostic enigma. Misdiagnosis or mishandling prior to referral makes the differentiation between other fungus infections, mycobacterial infections and neoplasia very difficult. Since treatment of each differs radically, accurate diagnosis is essential.

There are many reports of diagnostic delay in this disease.[4,6,8,11,12,14,16] The biopsy is important as a method of making early diagnosis so that appropriate therapy may be undertaken; however, cultures should be taken also, as either method may give false negative results. The examination of fresh aspirate is also not to be neglected. In our cases, we noted that both one or the other modality might be positive while the other is negative. In fact, in only two cases were both positive biopsy and positive cultures successfully obtained. Our study also reillustrates the futility of repeatedly subjecting the patient to inadequate courses of antibiotics. Of course, there has been speculation that there may be cases in which actinomycosis yields to a relatively short course of therapy without the diagnosis ever being made, and therefore is a more common infection than suspected, the reported cases being the tip of an iceberg.[2]

Actinomycosis may develop in a variety of anatomical sites. The disease may appear in the parotid gland, the maxillary antrum, the peridental areas of both jaws, the tongue, the submandibular gland, the skin of the face, the mastoid bone, and in the glands and deep tissues of the neck.[3,8,9,13,15,21] In our series, there were also several sites of infection; the process masqueraded as a variety of entities, which tended to obscure and delay the final diagnosis. Diagnosis was facilitated in those patients in which both incision and drainage for culture and removal of all or a portion of the infected tissue for biopsy was performed, though even this was not foolproof (Case 9).

Whereas it was once thought that it was acquired from grass, straw, and manure, it is now known that actinomyces is a common inhabitant of the oral cavity.[2,22] Through trauma to mucous membranes, through skin, or perhaps by the presence of bacterial invasion which facilitates the growth of the actinomyces, the infection may become established. Host factors, such as debility, immune suppression, and predisposing disease, such as diabetes, may be important, though this is not well illustrated in the literature. In our series, though the one patient who died had diabetes (Case 8), and one patient had prior carcinoma and radiotherapy (Case 15), the patients were likely as not to be apparently otherwise healthy. The host factors may be present, but are not easily demonstrated by presently available techniques.

Therapy of cervicofacial actinomycosis is twofold, including antibiotics and surgery. It appears to be generally an indolent type of infection, and it lends itself to surgical intervention without great danger. Advocates of surgery in these lesions stress the aim to more effectively eradicate the focus of infection and obviate the need for prolonged antibiotic therapy.[19] In our series, there were five cases in which multiple trials of antibiotics were used unsuccessfully, after which resection was done. Recovery was obtained subsequently with relatively short courses of antibiotics, Case 2 being an exception. In no case did a resection of the infected tissue appear to lead to systemic spread or to other harmful effects, with the possible exception of Case 8, the only patient who died. Certainly, as in the treatment of most abscesses, incision and drainage is not contraindicated, and may be the only method short of total excision that will afford a positive diagnosis.

Antibiotic therapy is the other prime modality in the treatment of actinomycosis. Penicillin is still advised as a first line drug by most authorities. Weese and Smith,[22] in their recent review, mention other modalities such as thymol, copper sulfate, and vaccines. They also note that potassium iodide, though effective against the Actinobacillus in cattle, does not affect the organism which infects man. Radiotherapy is also mentioned as outmoded. Dosages of penicillin recommended vary widely, but that recommended by Everts[6] is most characteristic; namely, 10-20 million units daily intravenously for two to four weeks, then five million units orally for three to six months. Sulfonamides and tetracyclines have also been widely used, as well as lincomycin and clindamycin. All these were used in this series as described previously. Clindamycin has been proposed as an alternate drug for patients allergic to penicillin or even as a primary drug of choice in all patients.[6,13] Considering its potential to cause colitis and the success of ourselves and others with the more familiar antibiotics, we would hesitate to recommend clindamycin before penicillin or the tetracyclines. Of course, we are dealing only with cervicofacial actinomycosis, which is more approachable surgically and perhaps less dangerous than the same infection in the thoracic or abdominal cavities. The one death in our series, in which actinomycosis was found in the liver, occurred after prolonged benzathine penicillin therapy—though it is difficult to conclude whether this illustrates the tenacity of the disease or the inadequacy of that modality of therapy.

SUMMARY

Actinomycosis is truly a masquerader, appearing in the head and neck in a number of guises, and resisting easy diagnosis. The diagnosis rests on a combination of careful techniques of microbiology and histopathology. Treatment is also a combined attack, using surgery—incision and drainage or gross excision—and antibiotics, in appropriate dosages and for sufficient duration. By these careful and considered methods, this masquerader can most often be unmasked and defeated.

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CLINICAL SIGNIFICANCE OF REBOUND NYSTAGMUS IN NEURO-OTOLOGICAL DIAGNOSIS

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SUMMARY — The present study is concerned with a clinical analysis of 17 patients with "rebound nystagmus" examined over a period of three years. All of them have shown a short duration second degree nystagmus evoked by changes in the direction of fixation, from the lateral to straight ahead gaze. This nystagmus was a fixation nystagmus, that is to say, it was enhanced in the presence of active optic fixation and inhibited in its absence. Almost all the patients (16 out of 17) had cerebellar signs on neurological examination (in one subject rebound nystagmus was the first sign suggesting cerebellar involvement and appeared several months before any other cerebellar sign was present). Rebound nystagmus was far more common than the other neuro-otological signs suggesting cerebellar dysfunction (vestibular hyperexcitability, dysrhythmia in postcaloric nystagmus and ocular dysmetria). In three out of four patients with unilateral lesions rebound nystagmus was ipsilateral with respect to the side of the lesion. Postmortem studies were carried out upon five cases and showed either pathological changes in the cerebellum or a lesion involving the cerebellar peduncles in the brain stem.

The role of cerebellar disease in the production of spontaneous nystagmus is still a controversial subject. The cerebellum receives projections from visual and ocular muscle receptor afferents, and sends efferent fibers to vestibular and oculomotor nuclei and to the pontine reticular formation. These connections make possible disturbances of oculomotor control in cerebellar disease.[1]

Holmes[2] was among the first to demonstrate the association of spontaneous nystagmus with lesions of the cerebellum. When studying a group of patients with acute lesions of the cerebellar hemispheres, he found spontaneous nystagmus on gaze toward the side of injury; this nystagmus was a fixation nystagmus, that is to say, it was enhanced in the presence of active optic fixation and inhibited in its absence. Recently, Westheimer and Blair[3] described a similar gaze-evoked nystagmus in monkeys after total cerebellectomy. Furthermore, Zervas[4] reported transient ipsilateral gaze-evoked nystagmus in man after a stereotactic surgery involving the deep cerebellar nuclei. This gaze-paretic nystagmus after acute cerebellar lesions soon subsides, due to compensatory mechanisms in the remaining cerebellum or brain stem.[1]

Cogan[5] considers that nystagmus is common in chronic cerebellar disease; a similar conclusion derives from an electronystagmographic study carried out by Jung and Kornhuber.[6] Brain and Wilkinson[7] report the presence of spontaneous nystagmus in 9 out of 19 patients with nonmetastatic subacute cerebellar degeneration associated with neoplasms. Victor *et al*[8] have found a fine horizontal nystagmus in patients with alcoholic cerebellar degeneration. Nevertheless, spontaneous nystagmus is not frequently observed in chronic cerebellar disease, and that is probably due to adaptation by the ocular motor control system to cerebellar dysfunction.[1] In this respect, Wania and Walsh[9] documented absence of nystagmus in a child two years after cerebellar ablation.

In a review of vestibular nystagmus, de Kleyn[10] reports on a special type of second degree nystagmus evoked by changes in the direction of fixation,

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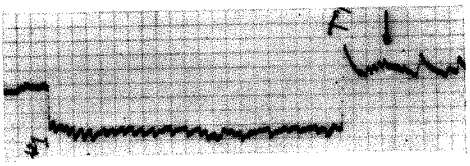

Fig. 1. Electronystagmographic recording of rebound nystagmus. The tracing on the left is a recording of the eyes in straight ahead gaze. Note the absence of spontaneous nystagmus in this direction of gaze. The tracing of the center corresponds to gaze deviation to the left, and a brisk spontaneous nystagmus to the left appears. The tracing on the right shows a return to straight ahead gaze with the appearance (arrow) of rebound nystagmus to the right.

from the lateral to straight ahead gaze; this nystagmus is of opposite direction to the one of the lateral gaze. It was found in 12 patients who were examined over a period of two years nevertheless, unfortunately no clinical information is given on such patients. Recently, Hood *et al*[11] studied 25 patients with the same type of spontaneous nystagmus, which they named "rebound nystagmus"; nearly all these patients had chronic cerebellar disease.

METHODS AND RESULTS

The present paper is based on the clinical analysis of a group of 17 patients examined over a period of three years (June 1972 - June 1975) in the neuro-otological departments of the Barros Luco-Trudeau Hospital and the Neurosurgery Institute. All of them were subjected to a complete neuro-otological assessment (which in many cases included electronystagmographic investigation) as well as neurological examination; in the case of certain patients it was necessary to make additional studies, such as pneumoencephalography, angiography, gamma scan, electroencephalography and other laboratory examinations.

None of our patients showed nystagmus in the primary position of gaze (that is to say, in straight ahead gaze); nevertheless all of them had spontaneous nystagmus in the lateral gazes, which was generally bidirectional. A common characteristic in all our patients was the appearance of a special type of second degree spontaneous nystagmus, produced by a sudden change in the direction of gaze. Thus with gaze deviation to the left a horizontal nystagmus to the left appears; nevertheless, if after keeping the eyes in such a position for a period of about 20 seconds the eyes are returned to the straight ahead position of gaze, a short duration second degree nystagmus to the right, not present initially, now makes its appearance. A similar (but opposite) phenomenon occurs with gaze deviation to the right. Following Hood *et al*[11] we have named it "rebound nystagmus" (Fig. 1). As with spontaneous nystagmus of central type, this type of nystagmus is inhibited or abolished when visual fixation is removed (Fig. 2). As it is observed in this figure, the inhibition of rebound nystagmus is only partial with Frenzel's glasses, and it is practically complete with eye closure.

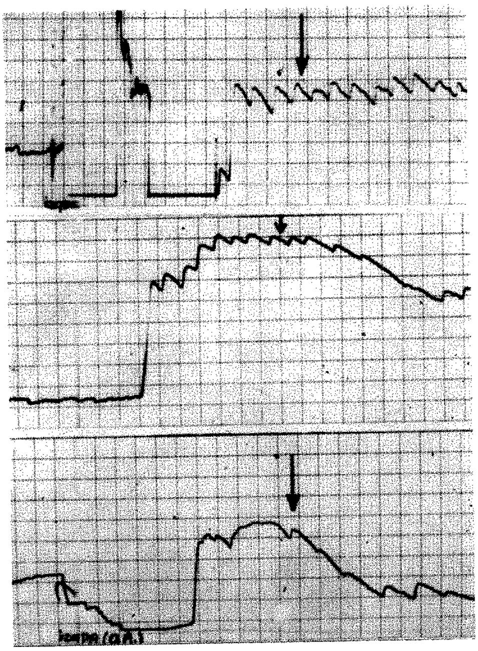

Fig. 2. Recording of rebound nystagmus to the right (arrows), when returning the eyes from the extreme left lateral gaze to straight ahead gaze. The upper record was made with ocular fixation (with eyes open), the central one with Frenzel's glasses and the lower one with the eyes closed.

Table 1 shows the diagnosis and the

TABLE 1. TYPES OF REBOUND NYSTAGMUS AND THEIR DIAGNOSIS

Case	*Type of Nystagmus*	*Diagnosis*
1	U	Bulbopontine astrocytoma*
2	B	Cerebellar hemispheres and right pontine tuberculomas*
3	U (from same side as lesion)	Right bulbopontine and thalamic gliomas*
4	U	Bilateral cerebellar astrocytoma*
5	B	Disseminated encephalomyelitis*
6	U	Parkinson's disease
7	B	Posterior fossa tumor
8	U	Multiple sclerosis
9	U	Neurosyphilis
10	B	Multiple sclerosis
11	U (from side opposite to lesion)	Right pontine lesion of vascular origin
12	B	Neurosyphilis
13	U (from same side as lesion)	Left posterior fossa gunshot wound
14	U	Multiple sclerosis
15	U (from same side as lesion)	Left Wallenberg's syndrome
16	U	Phenytoin®-barbiturate intoxication
17	B	Spino-opto-cerebellar degeneration

* - Proven at autopsy. U - Unilateral; B - Bilateral.

type of rebound nystagmus observed in each one of our patients. The analysis of their presenting symptoms shows that the unsteadiness was the most frequent complaint, and was present in 12 of the 17 patients (71%); nevertheless, in only half of them (6 patients) was this symptom associated with dizziness or vertigo. In opposition to the high frequency of the unsteadiness, it is curious to note that only three patients showed scanning speech.

All the patients showed spontaneous nystagmus and the latter was almost always bi- or multidirectional (only one patient, Case 15, had a unidirectional nystagmus). In 10 of the 17 cases (59%) there was positional nystagmus, which was of the central type in six patients and of the intermediate (that is to say, with central and peripheral mixed characters) type in the other four patients. Of the eight subjects in which it was possible to study the optokinetic nystagmus, this was altered in four of them. More than half of the patients (10 out of 17, that is to say, 59%) showed alterations in the caloric tests and it was possible to find the different types of abnormalities of caloric responses. Neuro-otological findings generally accepted as suggesting cerebellar involvement or of the cerebellovestibular connections in the brain stem (ocular dysmetria, vestibular hyperexcitability and dysrhythmia in postcaloric nystagmus) seldom appeared; only five patients (29.4%) showed dysrhythmia in postcaloric nystagmus; four (23.5%) showed ocular dysmetria (in one of them it was doubtful) and only two (11.8%) had vestibular hyperexcitability (in one of them it was doubtful). In neither of the two last cases was the vestibular hyperexcitability accompanied by dysrhythmia in postcaloric nystagmus.

Vermis and cerebellar hemispheres involvement was based upon evidence of truncal ataxia and ataxia of gait and the finding of muscular hypotonia, dysmetria, asynergia and dysdiadochokinesia. Sixteen out of the 17 patients showed neurological signs which indicated cerebellar involvement, the exception was one patient (Case 6) who suffered from Parkinson's disease. In acute contrast with the constancy of cerebellar involvement and vestibular alterations, in more than half of our patients (9 patients or 53%) there were no cranial nerve disturbances which might be indicative of a localization or extension of the lesion to the brain stem, or otherwise these disturbances were minimal.

In four patients (Cases 3, 11, 13 and 15) the lesion was clearly lateralized to one side of the brain stem and/or cerebellum. In three of these four patients (Cases 3, 13 and 15) rebound nystagmus was ipsilateral in respect to the side of the lesion, that is to say, it appeared when the eyes were returned from the lateral gaze corresponding to the side of the lesion to straight ahead gaze; in only one patient (Case 11) it was contralateral. From these findings it would seem that rebound nystagmus has a certain lateralizing value.

In five of our patients it was possible to make a later neuropathological study. Two of them (Cases 2 and 5) showed brain stem and cerebellar lesions; in one of them (Case 4) the tumor affected the whole of the cerebellum (vermis and cerebellar hemispheres), without damaging the brain stem, and in the remaining two (Cases 1 and 3) we found intrinsic brain stem tumors involving the middle and inferior cerebellar peduncles; in the last two patients the cerebellum was not involved. All these patients, therefore, showed either pathological changes in the cerebellum or a lesion involving the cerebellar peduncles in the brain stem.

DISCUSSION

In recent years a relationship has been established between overdosage by anticonvulsants, in particular, Phenytoin®, with disorders of balance.[12] The clinical picture may be acute, simulating a posterior fossa syndrome; in this case, the symptomatology quickly disappeared on discontinuing the drug. Nevertheless, a chronic imbalance is much more commonly encountered in patients treated with anticonvulsants during a long period of time.[13] Based on human postmortem examination as well as experiments on animals, Hofmann[14] found that in such cases the lesion responsible is a loss of the Purkinje cells of the cerebellar cortex. One of our patients (Case 16) was a 16-year-old woman who had been treated for some time due to an idiopathic epilepsy. Intending to commit suicide, this patient took approximately 3 gm of Phenytoin® together with a similar dose of Phenobarbitone®. The neuro-otological examination performed eight days afterwards revealed moderate imbalance, slight bilateral cerebellar signs, bidirectional spontaneous nystagmus and rebound nystagmus when turning the eyes from the left lateral gaze to straight ahead gaze. In a second neuro-otological examination, given one week later, there was no abnormality of stance or gait. Also the cerebellar signs, the spontaneous nystagmus and the rebound nystagmus had all disappeared. In this patient, the toxic effects of Phenytoin® were reinforced with intoxication with Phenobarbitone®, which has depressant effects upon the vestibular connections within the brainstem.[13]

Until recently, the only neuro-otological signs that suggested a cerebellar lesion or one of the cerebellovestibular connections in the brain stem were ocular dysmetria and certain alterations in postcaloric nystagmus, such as its dysrhythmia or the vestibular hyperexcitability (or hyperactivity).[15] Nevertheless, these signs only appeared in half of our patients with rebound nystagmus and were present in eight patients (47%). Of these, dysrhythmia in postcaloric nystagmus was the most frequently observed sign (it was found in five patients, 29%), alone or associated to ocular dysmetria; on the other hand, the vestibular hyperexcitability only appeared in two subjects (12%) and it was not associated to dysrhythmia in postcaloric nystagmus nor to ocular dysmetria. It follows from these findings that rebound nystagmus appears more frequently than the other neuro-otological signs suggesting cerebellar involvement.

Rebound nystagmus seems to be the most constant of the neuro-otological signs suggesting cerebellar involvement and at times it may appear before any other cerebellar finding revealed by a neurological examination. The latter was seen in one of our patients (Case 3), who was a 25-year-old man admitted to the hospital with symptoms of increased intracranial pressure; since all the examinations he had were normal, he was discharged with the diagnosis of a cerebral pseudotumor syndrome. Due to the persistence of the symptoms and the deterioration in his condition, he had to be readmitted. The neurological examination did not reveal any cerebellar sign; nevertheless the neuro-otological examination showed a bidirectional spontaneous nystagmus and, furthermore, a clear-cut rebound nystagmus when turning the eyes from the right lateral gaze to straight ahead gaze. We did not find ocular dysmetria, vestibular hyperexcitability, nor dysrhythmia in postcaloric nystagmus. Only eight months afterwards, and during a third readmission, the neurological examination showed bilateral cerebellar signs. After a certain period the patient died and the neuropathological study showed two brain tumors: a right thalamic anaplastic astrocytoma and a right bulbopontine (dorsolateral) infiltrative glioma involving the middle and inferior cerebellar peduncles. In this patient, therefore, rebound nystagmus was the first clinical indication of cerebellar involvement, and even it appeared before the neurological examination revealed any cerebellar sign.

The majority of patients studied by Hood *et al*[11] suffered from chronic cerebellar disease. In their opinion it remains to be established whether or not the lesion responsible can be localized within the cerebellum itself; nevertheless, they add, the available evidence appears to favor this view. Although the majority of our patients with rebound nystagmus also had chronic diseases, there were four patients (Cases 11, 13, 15, and 16) with acute lesions. In addition, the evidence derived from postmortem examination carried out upon five of our patients demonstrates that rebound nystagmus is a clinical sign of some significance indicating either damage of the cerebellum or a lesion involving the cerebellar peduncles in the brain stem.

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USE OF HEART RATE RESPONSE FOR THE ASSESSMENT OF HEARING IN INFANTS

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SUMMARY — The clinical utility of the heart rate (HR) response as an index of hearing in infant children under 12 months of age was investigated. The most prominent component of the averaged HR response elicited with a short tone burst of 100 msec duration was a brief HR deceleration which mostly occurred between the first and second beats after stimulation. The mean response detectability for tones of 250 Hz and 1 kHz were 50, 82 and 100%, with stimulations of 40, 60 and 80 dB above subjective threshold of normal adults, respectively. The detectability decreased a little at 4 kHz stimulation. Though there was an individual variability in the appearance of the response, the method was considered to be useful as a supplementary tool for evaluating hearing in infant children.

The heart rate (HR) response to auditory stimuli has been extensively explored in the field of experimental psychology, and a number of reports have been written on its use in the clinical evaluation of hearing.

In 1956, Zeaman and Wegner[1] measured the HR response to a mild auditory stimulation in four normal adults, and suggested the possibility of the response as an index of objective test of hearing in infants and uncooperative patients. Butterfield[2] studied HR change to a tone of 1 kHz at 40 dB above subjective threshold in three mentally retarded children and two normal students. He found no alteration in the HR of the mentally retarded children with the 40 dB tone, whereas a significant change in the HR was noticed in the normal subjects with the same auditory stimulation. Beadle and Crowell[3] examined auditory HR response in one full-term female neonate with modulated pure tones of 250 Hz and 6 kHz at the intensity levels of 40 to 60 dB. All tones were of 5 sec duration. However, the results were variable and no consistently discernible pattern of the HR response was obtained. Bartoshuk[4] reported on the basis of results obtained from 39 neonates that the absolute threshold for neonatal HR acceleration to a 1 kHz tone signal was between 38 and 48 dB SPL. Jasienska *et al*[5] studied HR changes in 35 newborns with tones of 500 Hz and 3 kHz at 90 dB, and proved evident responses in more than 80% of the cases tested.

Schulman and Wade[6] measured averaged HR change to band limited noises centered at 500 Hz and 3.6 kHz in 30 normal infants, and revealed that responses were obtained at the intensity of 34 dB SPL for most subjects. They stated that the most prominent response was HR deceleration with maximum change at approximately 6 sec after stimulus onset. Eisenberg *et al*[7,8] studied the HR responses to a train of 1.16 sec samples of the synthetic vowel "ah" at 60 dB. Most of the subjects were infants of 10 to 25 days of age. They compared the HR during each 10 sec immediately before and immediately after the stimulus onset, and found a sustained decelerative response. Griffiths[9] reported the usefulness of the HR response to the early identification of a hearing loss in infants. Her criteria for positive response is a deceleration of HR by four or five beats in 4 to 6 sec after onset of signal.

Reviewing all of the above mentioned studies on the audiometric use of the HR response, we feel that there

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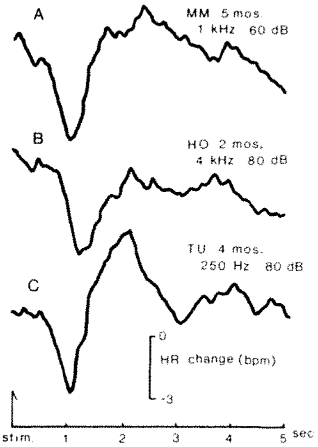

Fig. 1. Typical waveforms of the averaged HR response in three infant subjects. The upward deflection indicates an accelerative HR change. The secondary acceleration is most prominently recognized in Case C.

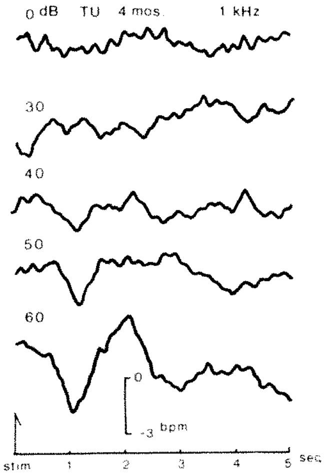

Fig. 2. HR response as a function of stimulus intensity. The response is detectable at stimulation levels of 40 dB and above.

is a marked difference among them in the method of auditory stimulation and data analysis, and in the interpretation of a positive response. The purpose of the present paper is not to investigate the auditory HR response *per se* but to find out a reliable and valid method for applying the response as a clinical tool for the assessment of hearing in infant children.

METHODS AND MATERIALS

Subjects were 16 infant children aged between one and ten months. All of them were found normal in physical examination and showed no suspicion of a hearing disorder. Informal consent to the test was obtained from the parents of the infants.

Electrocardiograms (ECG) were recorded through disk electrodes attached to the left lower leg and the right forearm by a biophysiograph (San-ei 180 system). ECG signals were fed into a cardiotachometer (San-ei, type 2130) for measuring beat-by-beat HR. As a rule, ten HR responses were averaged with a data processor (Nihon-koden, ATAC-201) and written out by an X-Y plotter (Yokogawa, type 3077). Trigger pulses coincident with stimulus onset and ECG were also recorded on a data recorder (TEAC, R-200) for further investigations. Pure tone of 250 Hz, 1 and 4 kHz were used as the auditory stimulus. The tones were produced with an audiosignal controller (Dana Japan, DA-505) and delivered binaurally to the subjects once every 15 sec through TDH-49 headphones. The duration of the tone was fixed at 100 msec with a rise-decay time of each 10 msec.

The infant was placed in an air-conditioned soundproof room and was tested during his natural sleep or sleep induced by an oral administration of triclofos sodium (70 mg/kg). Usually, the test tone was given from 20 to 80 dB above mean subjective threshold of normal adults by steps of 20 dB, if necessary, 10 dB.

RESULTS

Figure 1 illustrates typical waveforms of the averaged HR response elicited with short tone bursts. The most prominent and consistent component of the response is an abrupt and brief deceleration that is plotted on averaged traces to have a peak latency of 1 to 1.5 sec. Original tachograms revealed that this initial deceleration mostly occurred in the interval between the first and second beats after stimulus onset. The initial deceleration is usually followed by a slower acceleration with a maximum change at 2 to 3 sec after onset of stimulation. This typical pattern of the HR response closely resembles the newborn HR responses to click stimuli reported by Schachter *et al.*[10] They described three types of neonatal HR responses: 1) an initial deceleration followed by an acceleration (Fig. 1A, C), 2) deceleration alone (Fig. 1B), and 3) acceleration alone. Williams *et al*[11] stated that the pattern of the HR response to auditory stimuli varies significantly as a function of

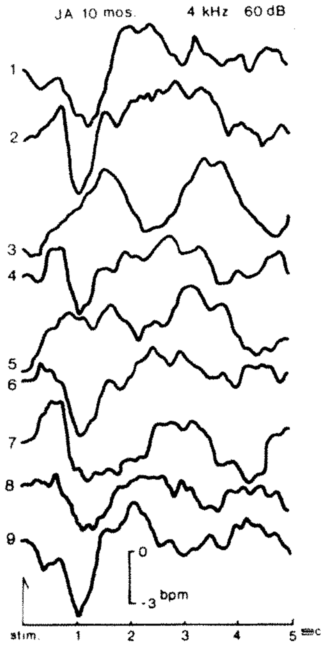

Fig. 3. HR responses consecutively recorded with the same auditory stimulation. The response is not present in Nos. 3 and 5, and equivocal in No. 7.

prestimulus HR slope. Note that the HR response with acceleration alone should be cautiously distinguished from spontaneous HR acceleration due to sinus arrythmia.

Figure 2 shows an example of the HR responses as a function of stimulus intensity. Though there were exceptions, the magnitude of the initial deceleration tended to increase and the secondary acceleration became more prominent as the stimulus intensity increased. Figure 3 presents nine consecutive averaged HR traces with the same stimulation of 60 dB. A significant inconsistency is found in the appearance of the response among these sequential traces. However, there is no tendency to habituation, that is, a gradual decrease in the magnitude of the response across the traces from first to ninth. In order to avoid false negative decision, it is essential to repeat the test two or three times with a given stimulus intensity when a clear response can not be obtained in the first trial.

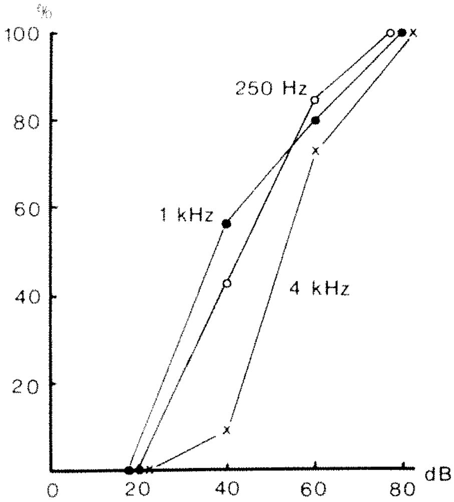

Fig. 4. Percentage of positive responses as a function of stimulus intensity.

Figure 4 shows the rate of positive responses as a function of stimulus intensity in 16 infants under 12 months of age. The HR response in this study seems to be less sensitive to 4 kHz tone than to 250 Hz and 1 kHz tones. The distribution of the HR response thresholds is presented in Figure 5. The response began to appear most frequently at 40 dB for tones of 250 Hz and 1 kHz, and at 60 dB for 4 kHz tone. The probability of making a false positive decision was low in the averaged HR

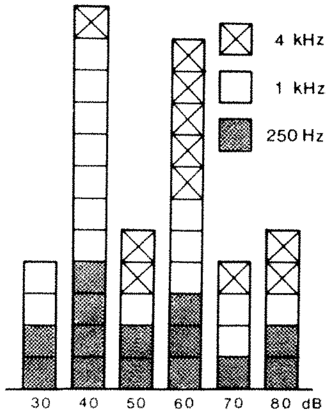

Fig. 5. Distribution of the HR response threshold. The histogram bar indicates the number of subjects.

traces under cautious judgment. Out of 40 traces taken from five infants without stimulation, false positive response was encountered only twice, the rate of this being 5.0%.

DISCUSSION

Our present study showed that the most feasible index of hearing in the HR response to brief tone stimulus is a HR decrease during the first and second poststimulus interval, followed by a slower acceleration. On the averaged cardiotachograms, this initial deceleration has a peak latency of 1 to 1.5 sec in infant children and is very easily detectable. Of course, the brief HR deceleration immediately following stimulation has already been observed in adults,[1,12-17] children,[18] infants,[19,20] and neonates.[10,11] Schachter *et al*[10] stated that the initial deceleration probably resulted from the increased vagal inhibitory activity which can decrease HR with sufficient rapidity to be effective within the 0.3 sec latency. On the other hand, a number of investigators who paid little attention to the transient HR change failed to observe the initial deceleration phase prior to the secondary acceleration. Therefore, it is no wonder that little has so far been discussed on the initial HR deceleration as an index of objective auditory testing.

Lang and Hnatiow[12] reported that the initial deceleration appeared to become more marked from the second to the fifth and tenth presentations of the stimulus and that it may be a reliable feature of the response after repeated presentations of the stimulus. Schachter *et al*[10] also stated that there was no evidence for the habituation in the initial HR response. The results in this study (Fig. 3) coincided well with them.

The mean detectabilities of the HR response to tones of 250 Hz and 1 kHz were 50, 82 and 100% at 40, 60 and 80 dB, respectively. These values closely approach those of the detectability of the slow vertex evoked response in the young child during sleep.[21,22] The response detectability at 4 kHz was a little lower than that for lower frequencies. Except for 4 kHz tone, the initial HR change to auditory stimulation is almost as sensitive as the slow vertex response and is within clinical feasibility. As Schulman *et al*[6] stated, the HR response has a number of advantages over the slow vertex response in evaluating hearing of infant children. The HR response is recorded with a simpler technique and can be detected more easily than the vertex response. The probability of false positive response in sleeping young subjects is far less in the HR response than in the vertex response. On the other hand, a drawback of the HR response is that the individual variability in the appearance of the response seems to be greater than that of the vertex response (Fig. 5).

The HR response is surely one of the promising indices for auditory testing of infant children. However, the interpretation of the response should be made with the greatest caution, and clinical judgment of a hearing impairment solely on the basis of an elevation of HR response threshold should be strictly avoided.

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HEAD AND NECK CANCER FELLOWSHIP

The American Society for Head and Neck Surgery is pleased to announce that it will sponsor a second fellowship in head and neck cancer at the M. D. Anderson Hospital beginning July 1, 1979. Applications are being accepted now and only until July 1, 1978. The fellowship carries an award of $5,000 in addition to the usual stipend for residents and fellows at the M. D. Anderson Hospital. For further information write: James R. Chandler, MD, Chairman, Fellowship Committee, American Society for Head and Neck Surgery, P. O. Box 520875, Miami, FL 33152.

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RESULTS OF NEW AIR CALORIC TESTING METHOD AMONG NORMAL SUBJECTS. I. BIPHASIC TESTING

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ROLLIN C. DIX, PhD
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SUMMARY — A new air caloric testing method is described in which the temperature of a continuous aural irrigation is switched between hot and cold values at times calculated to control the intensity of the resulting vestibular stimulation. Applications of low or high caloric stimulus intensities to normal subjects were well tolerated and reliably produced appropriate low or high intensity nystagmic responses. Nystagmus intensity values obtained from this study were compared with predicted intensity values from a computerized simulation of the actual test conditions, and also with values obtained when using biphasic water irrigations. As a result, further improvements in our methodology have been effected.

Currently, the primary clinical method for testing the vestibular system is the caloric test. This test consists of the instillation of a fluid into the external auditory canal to induce temperature changes in the labyrinth area and thereby stimulate the vestibular receptor. The standard method commonly used in clinical situations is the one described by Fitzgerald and Hallpike in 1942,[1] using sequential water irrigations at 30 C and at 44 C in each ear.

There are several characteristics of this procedure which may be considered disadvantageous. First, the conventional caloric stimulus is too prolonged, causing some patients to experience fatigue or nausea. Second, the complete examination requires an excessive amount of time, due to the fact that a waiting period of ten minutes between irrigations is necessary in order to prevent a given response from being influenced by a residual effect from a preceding irrigation. This requirement is substantiated by evidence which indicates that the stimulus caused by a conventional caloric irrigation continues for more than ten minutes and persists well beyond the time when nystagmus usually ends.[2,3] Furthermore, the most precise correlation between nystagmus response intensity and stimulus strength has been shown to be obtained by measuring slow phase eye speed at the peak of the response and not by measuring duration of response,[4] so there is no compelling reason for monitoring nystagmus much beyond the point of maximal response. Finally, there is at present no convenient and precise method for adjusting the intensity of the conventional caloric stimulus.

We have developed a vestibular testing method which is designed to overcome these disadvantages. Certain practical difficulties when using water irrigations have prompted us to substitute air as the irrigation fluid, employing an air stimulator described in a separate report.[5] The air stimulator consists of an air-water heat exchanger in which a stream of air is brought to a desired temperature set point by passage through a waterjacket, the latter being controlled by a constant-temperature water circulator. With certain modifications, air irrigations have been introduced for routine use in many clinical vestibular laboratories. For example, Capps *et al*[6] found that using 60-second air irrigations at 24 C and 50 C en-

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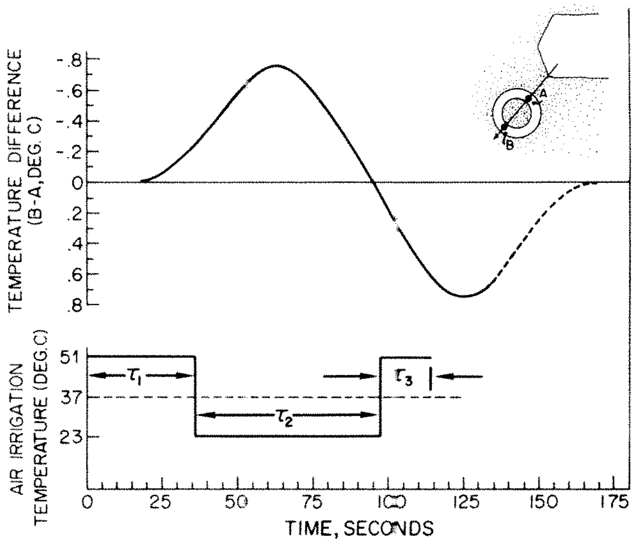

Fig. 1. The temperature difference across the lateral semicircular canal (B-A, upper figure) is predicted to follow a smooth, roughly sinusoidal course as a result of step temperature changes during continuous aural irrigation with air. The air irrigation temperature sequence required for this stimulus pattern is shown in the lower graph. t_1, t_2, t_3: irrigation durations (see text). Note that the temperature difference reaches equal peak values (±.75 C) during the hot and cold phases of the reaction. (Reprinted by permission, Trans Am Acad Ophthalmol Otolaryngol, 1976.)

abled them to produce responses equivalent to those produced by conventional 30-second water irrigations at 30 C and 44 C.

In earlier studies,[7,8] we demonstrated that certain objectionable features of the Fitzgerald-Hallpike method of irrigation can be overcome by switching the temperature of a single water irrigation between hot and cold values, thereby bringing the hot and cold stimuli into apposition. The result is a hot stimulus followed immediately by a cold stimulus and then a prompt removal of all caloric stimulation. The method for controlling and balancing the hot and cold phases of this new biphasic caloric stimulation procedure is based upon mathematical predictions of heat conduction in the labyrinth area, as explained below. The present report describes our experiences when using air irrigations, instead of water, to perform the new test procedure. Taking into account the differences in thermal properties between air and water, we computed new parameters for the test stimulus. In preliminary tests among normal subjects, we found that nystagmus responses were in good agreement with the predicted stimulus profile.[9] The present experiment was designed to investigate more precisely the character and range of responses to the new biphasic air caloric test procedure, to determine whether selected changes in the intensity of the biphasic stimulations would have a significant and predictable influence on the response intensity, and to explore the relationship between response intensities and physical dimensions of the test subjects.

THEORETICAL CALCULATIONS

Aural irrigation with cold or warm fluid causes a temperature difference to appear across the labyrinth, attended by changes of endolymph density, thereby providing the basis for stimulation of the vestibular receptor by convection displacement of the endolymph-cupula system. The temperature difference primarily affects the lateral semicircular canal[1,10-12] and thus the intensity of the nystagmic response to caloric tests can best be predicted from a knowledge of the stimulus acting on

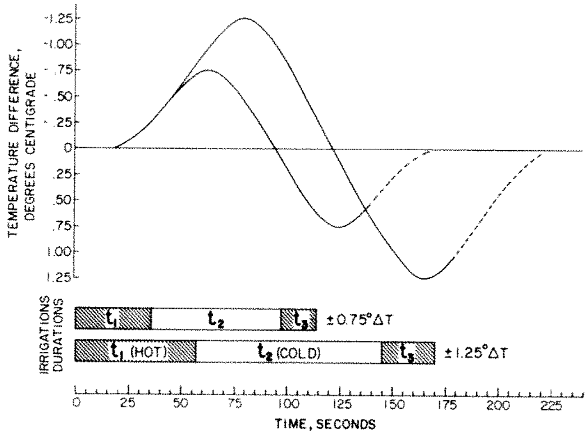

Fig. 2. Time profiles of the caloric stimulation intensities used in the present report. The shorter irrigation durations (t_1, t_2, t_3) produce the lower amplitude curve (*low* stimulus = ±.75 C ΔT) and the longer irrigation durations produce a higher amplitude curve (*high* stimulus = ±1.25 C ΔT).

this particular canal. The magnitude of endolymph-displacing forces developed by the caloric test is nearly proportional to the temperature difference across the semicircular canal as long as the orientation of the canal with respect to gravity is controlled.[10] Therefore, a knowledge of the temperature difference across the lateral semicircular canal permits a direct estimation of the intensity of the caloric test stimulus.

The temperature difference across the lateral semicircular canal (ΔT) may be calculated using a mathematical model of unidirectional conduction of heat through a homogeneous solid.[11] Furthermore, if the irrigation fluid temperature is switched abruptly between hot and cold values, the timing of this temperature switching can be used to adjust and control the intensity of the caloric stimulus at the lateral semicircular canal[7,8] (Fig. 1).

We used a 51 C air irrigation which was interrupted by quickly switching the temperature of the irrigation to 23 C, and then switching back to 51 C. Under these conditions the duration of the initial 51 C irrigation (t_1) determines the intensity of the caloric stimulus produced during the initial hot phase of the stimulation. In a similar way, the duration of the cold irrigation (t_2) determines the intensity of the resulting caloric stimulus during the cold phase. Finally, the cold phase is terminated by a brief irrigation at the hot temperature (t_3). Values for t_1 and t_2 have been calculated by means of a computerized search procedure,[13] using the mathematical model mentioned above. We used the values for physical parameters as determined by Young,[11] except for a 30% reduction in the heat transfer coefficient, a modification based on our preliminary trials among normal subjects.

Our goal was to adjust the duration of the irrigation sequence (t_1, t_2, t_3) in such a way that hot and cold stimulations of equal intensity would be produced, followed by prompt and complete removal of the caloric stimulus. Figure 1 shows the predicted curve for caloric stimulus intensity caused by irrigation at 51 C for 36 seconds (t_1), switching to 23 C for 61 seconds (t_2) and then briefly back to 51 C (t_3).

The computerized search procedure described above was used to determine sets of values for irrigation durations t_1 and t_2 required to produce a graded series of stimulus magnitudes. These calculations indicated that caloric stimulus intensity could be controlled and adjusted in a consistent manner by simply selecting the appropriate set of irrigation durations. For example, the

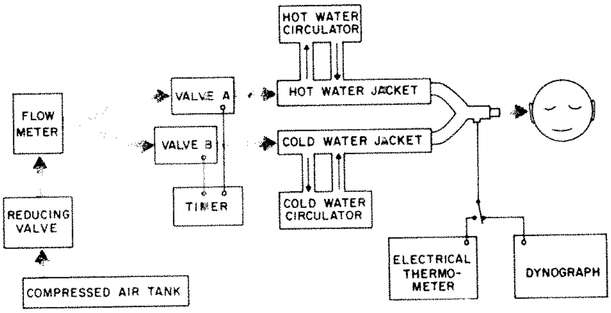

Fig. 3. Diagrammatic representation of apparatus for switching air irrigation temperature between hot and cold values at preselected times (see text). (Reprinted by permission, Trans Am Acad Ophthalmol Otolaryngol, 1976.)

two stimulation intensities used in the present experiment are shown in Figure 2, along with an indication of the irrigation fluid temperature sequences required for their production. Our calculations indicated that a wide range of stimulation intensities could be produced by adjusting t_1 and t_2 values. An upper limit of stimulation intensity is approached as values for t_1 approach 336 seconds and peak ΔT values approach 3.06 C.

METHODS AND MATERIALS

In order to apply the new air stimulation technique, it was first necessary to assemble the appropriate equipment. The outflow from two air stimulators[5] was fed into a common nozzle (3 mm I.D.) so that the air irrigation could be switched quickly between hot and cold values[9] (Fig. 3). During operation of this apparatus, dry air at a flow rate of 8 liters per minute was passed through either the warm or cold water jacket, depending on the setting of electrically operated valves. The valves were controlled by an electrical timer so that air flow could be started and directed through either the hot or cold water jackets at appropriate times. A temperature sensor within the nozzle, 8 mm from the orifice, allowed constant monitoring of the air stream temperature at a point just before it entered the ear canal. The nozzle orifice was held in a position about 5 mm into the external auditory canal and the stream was aimed by direct vision at the posterosuperior quadrant of the tympanic membrane anulus. A readout for this temperature sensor was registered on one of the channels of the dynograph used for recording nystagmus. In this way, an accurate reading of air irrigation temperature at any given moment could be made from the dynograph record.

Subjects were interviewed prior to testing and eliminated from the series if they had a history of ear disease, ear surgery, head injury, vertigo (including motion sickness), recent drinking or smoking, or if they were receiving medication of any kind. Subjects' ears were examined and cleansed of excess cerumen, if present, under microscopic control. Aural canal cross-sectional dimensions were estimated by comparison with calibrated ear speculae and skull sizes were measured with calipers. Body temperature of subjects and room temperatures during the test sessions were recorded.

The same standard explanation was given to each subject prior to electronystagmographic (ENG) testing. Preliminary ENG studies consisted of standard calibration, ocular pursuit movements, mental alerting with eyes closed to test for spontaneous nystagmus, and positional testing, including head hanging. If there was evidence of abnormal response to these preliminary tests, the subject was eliminated from the series. During irrigations, each subject was instructed to notify the tester of any discomfort or sensation of movement. Mental alertness was stimulated during the period of predicted peak response for a period of 30 seconds by having the subject count backward aloud by sevens. Variability of the corneo-retinal potential was reduced to a minimum by having the subject keep his eyes open between irrigations, and by performing the testing session in a dimly lit room.

We used biphasic air caloric irrigation sequences that were predicted by calculation to produce peak temperature differences across the lateral semicircular canal of ±0.75 C and ±1.25 C (Fig. 2). The former is represented as the *low* stimulus, the latter is represented as the *high* stimulus. Three biphasic stimuli were presented to the right ear of each subject with a waiting period of ten minutes between the onset of successive irrigations. All possible orders of test presentation which included at least one *high* and one *low* stimulus were used, assigning test sequences to subjects randomly (Table 1). Ten minutes after the final right ear irrigation, three consecutive *low* stimulations were applied to the left ear, at six minute intervals. This was done to see whether there was evidence of unilateral hypoexcitability or directional preponderance.

The response to caloric stimulation was recorded by ENG (Fig. 4) with amplitude cali-

TABLE 1. RESPONSE INTENSITY SCORES RESULTING FROM *HIGH* AND *LOW* STIMULATIONS OF RIGHT EARS (HOT RESPONSE/COLD RESPONSE, °/SEC)

Subj.	*Stimulus Strength*	*Responses* *Test 1*	 *Test 2*	 *Test 3*
A	Low, High, Low	6.95 (Hot) 4.14 (Cold)	8.59 3.85	4.14 2.92
B	High, Low, High	13.69 7.72	6.26 3.83	14.91 7.77
C	High, Low, Low	37.76 17.57	10.91 5.98	9.47 3.74
D	Low, High, High	9.17 9.09	20.5 18.24	24.73 24.12
E	Low, Low, High	19.51 14.52	21.79 10.32	30.94 18.33
F	High, High, Low	12.72 11.32	7.21 10.58	5.74 6.20

bration performed immediately before and after each caloric irrigation. Nystagmus intensity was scored by measuring slow phase eye speed of each nystagmus beat, utilizing a mechanical slope plotter.[14] Eye speed measurements were then averaged over five-second periods and these mean values were used for plotting responses, as shown in Figure 5. Next, two representative scores for response intensity were computed by averaging slow phase eye speed during the most intense 20 seconds of the hot phase and the cold phase of each response (Table 1).

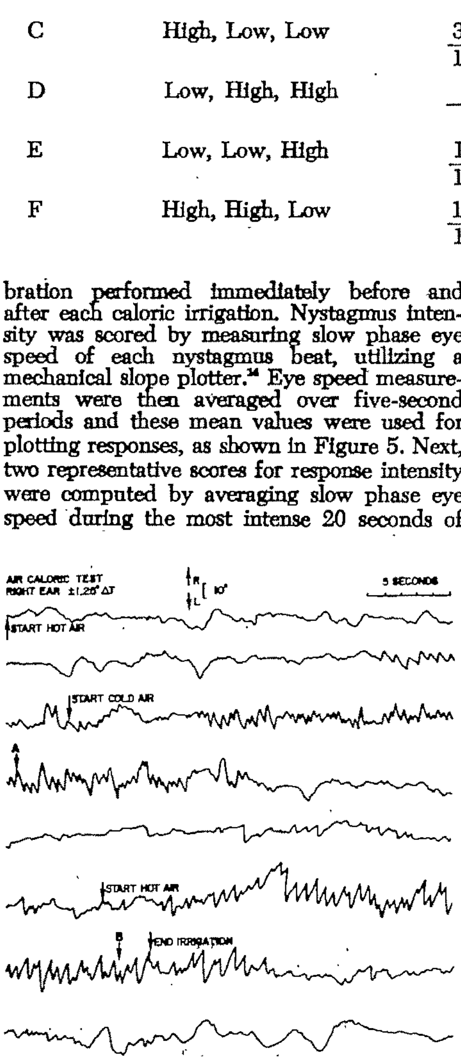

Fig. 4. Eye movement record (ENG) of nystagmus induced by *high* biphasic caloric stimulation in normal subject. Times of irrigation events are indicated. Note that nystagmus towards the irrigated ear reaches a peak intensity at the predicted time, A, passes through a null period and reaches a second peak intensity beating in the opposite direction, at B.

RESULTS AND STATISTICAL ANALYSIS

The pattern of responses to the new test procedure generally conformed to a biphasic, bidirectional nystagmus pattern that would be expected from such a stimulus. A typical response is shown in Figure 4. As can be seen in the figure, nystagmus begins towards the irrigated ear (hot caloric response), reaches a peak intensity at about the same time as predicted by our calculations (Fig. 4A) and then subsides. Following a brief null period nystagmus appears in the opposite direction, again increased in intensity to reach a peak close to the predicted time (Fig. 4B) and then once more quickly subsides. Nystagmus intensity averaged during each five seconds of this response is indicated in Figure 5, along with the predicted temperature difference curve. It can be seen that these values follow the predicted curve quite faithfully. However, we found that among most subjects the second (cold) phase of the nystagmus usually reached a somewhat lower peak intensity and subsided more rapidly than predicted by the mathematical model. To investigate further the question of whether we had achieved our goal of balanced hot/cold stimulus intensities, the average time courses of all responses from each of

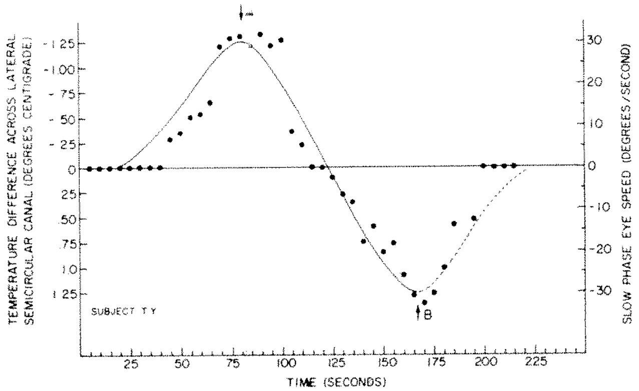

Fig. 5. Plot of average slow phase eye speed during 5-second intervals of response shown in Figure 4. Positive and negative eye speed values indicate nystagmus directed toward the same or opposite ear, respectively. The *high* stimulus intensity curve from Figure 2 is superimposed for comparison.

the tests (high stimulus, right; low stimulus, right; and low stimulus, left) among the six subjects were determined and plotted (Fig. 6). The results show a hot/cold disproportion in each case. We feel this imbalance is the result of a discrepancy between an abrupt switching of irrigation temperature from hot to cold, assumed in our calculations, and the slower temperature change actually produced by our stimulator (see "Hardware Design").

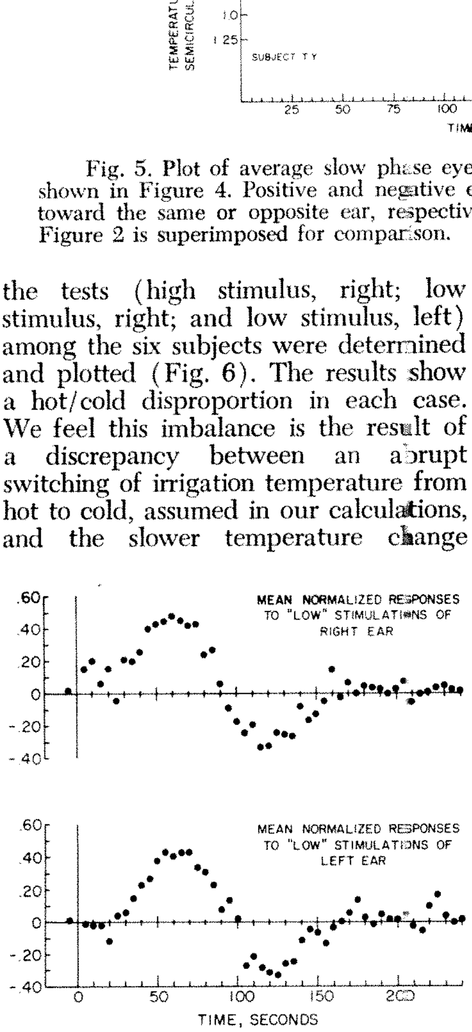

Fig. 6. Average normalized slow phase eye speed scores from 5-second intervals of responses to *low* stimulations. Each subject's scores were normalized in respect to his single highest score. Data includes 9 responses from right ears and 18 responses from left ears. Note that hot phase responses were more intense than cold phase responses in both the right and left ears.

Nystagmus intensity scores for the hot and cold phases of right ear responses are shown in Table 1. Statistical analysis was performed on the natural logs of the data and subjects were treated as a random sample from a population. The effect on responses of changing stimulus strength from *low* to *high* was highly significant. The best estimate of the difference in response between the two conditions (*high* stimulus and *low* stimulus) is a 110% increase in response to *high* as compared to *low*. The order of presentation of stimulations was found to be not statistically significant.* None of the following variables was found to have any significant correlation with response intensity: Anterior-posterior skull size (range = 18.0-20.0 cm); intermastoid skull size (range = 12.5-14.2 cm); ear canal size (range = 5.0-6.0 cm); age (range = 19-23 years); subject temperature (range = 36.3 C-37.1 C); room temperature (range = 26.4 C-27.1 C); and sex (two males, four females).

Responses to the three *low* stimulations of the left ear were also scored. The intensities of induced nystagmus were compared in the conventional manner to rule out subject abnormali-

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*Statistical calculations and tables are available from the author by request.

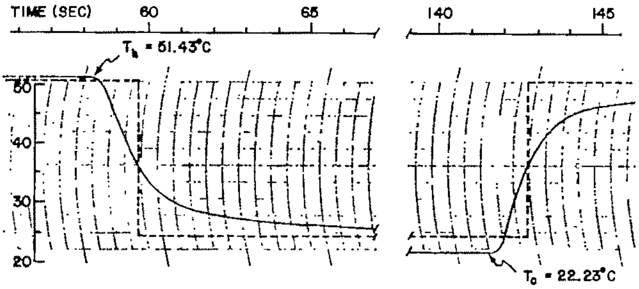

Fig. 7. Actual record of air irrigation temperature (solid line) which produced response shown in Figures 4 and 5. T_h, T_c: points at which final hot and cold irrigation temperatures were measured. Broken line indicates step-wise change in irrigation temperature assumed in our preliminary calculations. The discrepancy between these curves must be taken into account when calculating switching times (t_1, t_2, t_3) and predicting the course of the physical stimulus ($\triangle T$).

ties. For these calculations we used only responses to *low* stimulations, since these were the stimulus levels common to both ears. The response data was entered into the standard formulas for unilateral canal hypoexcitability and for directional preponderance.

Evaluation of the responses in this manner ruled out any consistent trend in the unilateral hypoexcitability or directional preponderance scores. It was also encouraging to find that the temporal profile of mean normalized responses of the left ear was quite similar to the profile from the right ear in spite of the shortened waiting period between irrigations (Fig. 6) (comparative data tables are available).

In order to assess the reliability of slow phase eye speed measurements, we rescored portions of several responses. Values for slow phase eye speed in degrees per second, measured for individual nystagmus beats during the original scoring, were compared with values obtained during a second scoring of the same records performed by the same scorer. The estimated standard deviation of the percentage error of any single measurement was 13% overall. This, however, varied with the value of the slow phase eye speed, being 17% for readings less than 10°/sec and 9% for readings greater than 10°/sec. This 13% error should be greatly reduced when applied to the measurements in this study, since we used the mean slow phase eye speed reading averaged over 5-second periods and over 20-second periods.

HARDWARE DESIGN

It is important to discuss the performance characteristics of our biphasic air stimulator in order to facilitate interpretation of our data and to guide those who might wish to duplicate the method. The temperature and switching times of air irrigations were monitored by displaying the air stream temperature on the ENG tracing (Fig. 7). In order to determine how precisely we reproduced the irrigation temperature sequences during each test, we measured the air irrigation temperature at the end of the hot and cold phase of all irrigations (T_h and T_c, respectively, Fig. 7) and checked the duration of each irrigation sequence. Only insignificant variations in these durations were found.

A broken line in Figure 7 indicates the step-wise changes in air irrigation temperature (T_{ir}) assumed for determination of switching times and prediction of the physical stimulus profile at the outset of this study. As can be seen, our equipment did not produce the ideal square wave temperature profile. Therefore, the time course of the physical stimuli ($\triangle T$) presumably differed from the curves shown in Figures 1 and 2. Using the model of heat conduction in the temporal bone,[11] we introduced actual irrigation temperatures to a computer simulation and computed the expected $\triangle T$ curves for the *low* (.75 C) and *high* (1.25 C) irrigation sequences.* The resulting values showed the cold phase peak to be consistently lower than the hot phase peak for both *high* and *low* sequences. These results indicate that the inequality of hot and cold peak responses can be attributed to time lags in temperature switching from hot to cold (Fig. 7, solid line). Thus it appears that the hot/cold disproportion shown in Table 1 and in Figure 6 is explained by the performance characteristics of the air irrigation hardware. We believe a solution to the problem of balancing the intensities of the hot and cold phases of stimulation will be found by basing the computation of switching times on measurements from the actual irrigation temperature profile produced by the air stimulator.

An additional observation is of interest. Based on computer simulations with trials using various values for the heat transfer coefficient (h) to correct for the differences in nystagmus intensities produced by air irrigations during the present study, and intensities produced by water irrigations in the previous studies,[7,8] the value for the air heat transfer coefficient should be further reduced to $H = .735 \times 10^{-3}$ cal/cm^2/sec/C.

In summary, hardware to be used in the performance of this new test procedure should provide, above all, a precisely repeatable irrigation temperature switching profile. The profile should conform as closely as possible to the ideal step-wise pattern. Finally, computation of switching times (t_1, t_2, t_3) should be based on the irrigation temperature profile actually produced and an h value of $.735 \times 10^{-3}$.

DISCUSSION

The primary advantages of this new irrigation technique are to be found in the reduced duration of action of the caloric stimulus and the practical and convenient method for adjusting the intensity of individual stimulations. The technique can be put to good use for research purposes as well as in a clinical setting. The prompt removal of caloric stimulation after a selected peak stimulus has been reached permits a reduction in the waiting time between irrigations as well as reducing the possibility of interaction among successive stimulations. Although two subjects found the induced vertigo moderately unpleasant, no subject experienced any distressful side effects such as nausea, from the levels of stimulation used.

Statistical evaluation of our data has enabled us to show that a moderate adjustment of predicted stimulus strength reliably produces a significant change in response intensity among normal subjects. The exact relationship between adjustments of stimulus intensity and induced nystagmus intensity will, of course, become more evident with further investigations. In general, we have found that the time course of nystagmus intensity conforms to the predicted time course of the stimulus intensity (Fig. 5), except for a minor deviation (Fig. 6) which presumably can be corrected by modification of hardware design or irrigation timing.

Utilizing statistical calculations designed to test for order effect, no evidence could be found that any one irrigation exerted an influence on any subsequent irrigations, regardless of peak levels achieved. This lack of order effect was also demonstrated when a lower stimulus level was applied at six-minute intervals.

Rescoring records showed measurement errors ranging from 9% to 17%. The fact that percent error was in the lower range when nystagmus responses were greater than 10°/sec is important because our statistical calculations were based on data from the point of peak responses, where a slow phase eye speed usually remained above 10°/sec. Another important factor is that reliability of measurement of slow phase eye speed is increased by averaging.

CONCLUSIONS

This study has confirmed the practicality of the new caloric testing method when using air, instead of water, as the irrigation medium. We have also shown that application of two different caloric stimulus intensities reliably produced appropriate differences in nystagmic response intensities. Experience gained in this study has provided a basis for a major re-estimation of the heat transfer coefficient for air during aural irrigation.

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*Heat transfer coefficient used was 1.47×10^{-3} cal/cm^2/sec/C.

In general, the time course of nystagmus intensity followed the predicted time course of the physical stimulus. However, the average intensity of nystagmus during the hot phase of the reaction definitely exceeded that of the cold phase. This imbalance was shown to be due to a deviation of the actual irrigation temperature profiles from the ideal square wave pattern. Since it may not be possible to achieve true square wave switching of irrigation temperature, we plan to incorporate data from actual irrigation profiles into our future calculations of switching times (t_1, t_2, t_3). In this way, switching times can be adjusted to bring the caloric stimulus intensity to the desired level. It should be pointed out that the air stimulator used in this study performed quite satisfactorily in respect to the requirement that irrigation temperatures and switching profiles be consistently and precisely repeated for each successive test.

The implications of our findings are encouraging. In its present state of development, this new test method provides a practical means for adjusting the intensity of the caloric stimulus and improving the convenience and acceptability of the procedure.

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CHORIOCARCINOMA OF THE NOSE

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SUMMARY — A case of choriocarcinoma in a 17-year-old unmarried female is presented. She attended the E.N.T. Clinic with a rapidly growing mass at the tip of the nose. Histologic report of the excised mass was reported as a secondary deposit from a choriocarcinoma. Further questioning at this stage revealed the history of an abortion two years before. Gynecological examination revealed secondary deposits in the vagina. X-rays of the chest showed evidence of metastases in the lungs. She died of profuse bleeding from the vagina.

Choriocarcinoma is an epithelial malignancy of trophoblastic cells first recorded by Sanger in 1889 under the title "malignant metastasizing deciduoma."[1] Marchard[2] in 1898 introduced the term "chorion-epithelioma" and demonstrated that the tumor cells originate from epithelial cells covering the chorionic villi.

The reported incidence of choriocarcinoma varies widely in different centers from 1 in 40,000 pregnancies in England[3] to as high as 1 in 953 in India,[4] and 1 in 483 in Taiwan.[5] It is preceded by hydatidiform moles (50% of reported cases), previous abortions (25% of reported cases), normal pregnancies (22%), and in ectopic gestations and genital and extragenital teratomas in 3% of cases.[6]

Spread of the tumor is almost entirely by the bloodstream, owing to the fundamental tendency of trophoblastic cells to invade blood vessels. Distant metastases may occur at an extraordinarily early time after an abortion. Favored sites of involvement are the lungs (50%) and vagina (30 to 40%), followed in descending order of frequency by the brain, liver and kidney.

Although any organ or tissue may be involved in the dissemination of this neoplasm through the bloodstream, a secondary deposit of choriocarcinoma in the nose is a nearly unknown entity. A medical literature search[7] carried out by the World Health Organization in Geneva found only one reference of a chorionepithelioma in the nose in the last ten years.[8]

The present case is very interesting in that it presented as a neoplasm of the nose with absolutely no gynecological complaints. The diagnosis was made on the basis of histological report of the excised mass, corroborated later by gynecological examination findings, urinary chorionic gonadotrophin test, and from a positive clinical history of abortion, obtained with difficulty.

CASE REPORT

A 17-year-old unmarried female attended the E.N.T. Clinic of the University of Nigeria Teaching Hospital, Enugu, with a four-week history of a rapidly growing mass at the tip of the nose, bleeding to touch and slight trauma (Fig. 1). On examination, the mass measured 4 by 4 cm, the tip ulcerated, partly necrotic, arising by a broad base from the vestibule, tip and the columella of the left nostril. No view of the inside of the left nostril was obtained. The right nostril was free. There was no significant enlargement of cervical lymph nodes.

X-rays of the paranasal sinuses did not show any bony involvement. X-rays of the chest revealed a rounded large shadow in the midzone of the left lungfield. A clinical diagnosis of angiosarcoma with secondary deposits in the left lung was made.

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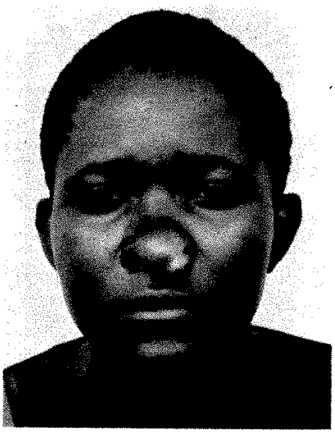

Fig. 1. Seventeen-year-old female with mass at tip of the nose.

Blood examination at this stage revealed a hemoglobin level of 10 gm %, WBC of 7,800 cu mm with normal differential count. ESR was 22 mm/first hour. Her blood was cross-matched; she was group O Rh(D) positive.

On November 23, 1976, she was operated. The mass was removed almost completely in one piece, although a total clearance was not achieved. The neoplasm was found to be infiltrating the surrounding tissues, particularly the tissues near the tip of the nose. There was fairly profuse bleeding controlled by continuous silk sutures. The mass was sent for histologic examination.

The histology report, available on the fifth day, came as a complete surprise. It was reported as "hemorrhagic necrotic tumor tissue with sheets of syncytial and cytotrophoblastic cells showing pleomorphism and anaplasia. Diagnosis—metastasis from choriocarcinoma" (Fig. 2).

With this diagnosis, the patient was questioned further and she revealed, after considerable difficulty, that she had been pregnant two years before and had had an abortion carried out by a "native doctor." On gynecological examination the uterus was found to be bulky, with secondary deposits in the suburethral area and also on the posterior vaginal wall, size 3 cm in diameter. There was offensive blood-stained discharge from the vagina. A urinary chorionic gonatrophin test was carried out and was found to be moderately positive.

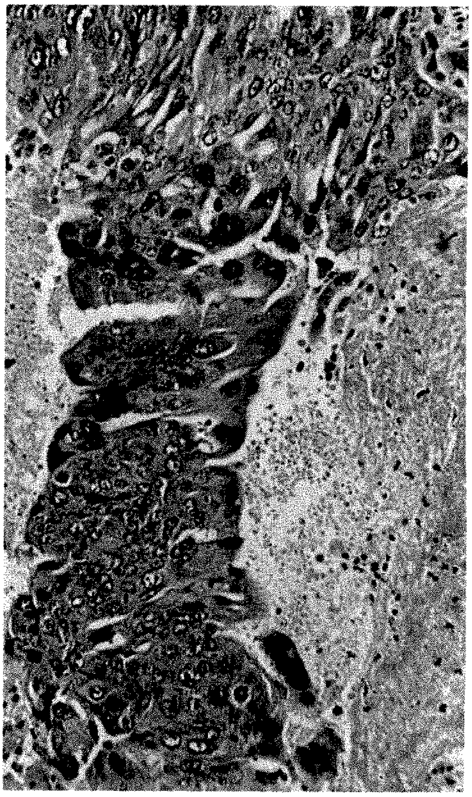

Fig. 2. Hemorrhagic necrotic tumor tissues with sheets of syncytial and cytotrophoblastic cells showing pleomorphism and anaplasia (H & E, X180).

She was put on oral methotrexate 20 mg daily. Six days after the operation, she developed nodules (2 by 2 cm) in the substance of each breast and had bouts of nausea and vomiting indicating possible intracranial involvement.

She received 1.42 liters of whole blood but even then the blood examination on the tenth day postoperative showed a hemoglobin level of only 6 gm %. Platelet count was 350,000/cu mm. WBC total count was 9,350/cu mm with neutrophils 71%, eosinophils 2%, lymphocytes 22% and monocytes 5%. She then received another .95 liters of blood.

She continued to fail and died on the 14th day postoperative following a bout of very profuse bleeding from the vagina. A postmortem examination could not be carried out as permission was not granted by the relatives on religious grounds.

DISCUSSION

This case is interesting in several respects. There were initially no presenting gynecological complaints at all. The patient was investigated gynecologically *only after* the histology report. The findings were classical.

1. The patient had had an abortion two years before by a layman.
2. She had metastases in the lungs. (This occurs in 50% of all reported cases of choriocarcinoma.)
3. She had metastases in the vagina. (This is found to occur in 40% of all reported cases.)
4. She had possible intracranial metastases.
5. Urinary gonadotrophin test was positive.
6. Histology findings were diagnostic.

The most interesting aspect of this case was that the patient presented with the secondary neoplasm in the nose, a condition reported only once before in the world literature.

It is regrettable that a postmortem examination could not be done as this would have revealed interesting findings, no doubt.

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EARMOLD CONFIGURATION: RELATION TO SPEECH DISCRIMINATION SCORES

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SUMMARY — Choice of the earmold for a particular individual is perhaps the most subjective of all decisions made by clinicians in hearing aid fitting. The four earmold designs used in this study were standard-long, standard-short, belled-vented, and cavernous. Conclusions were: 1) performance differences in earmolds of contrasting design can be assessed by discrimination scores with monosyllabic word lists of equal difficulty; 2) among the physical measures taken of the earmold-receiver systems, frequency-response overall range (HAIC) ranked the devices in agreement with group responses to a word identification task; and 3) these data offer a basis for endorsement of the standard-long and cavernous-short earmold types over the other two with their superiority evident in each of the discrimination categories of excellent, good, and poor.

One of the hearing aid components, which for decades was given secondary importance, is the earpiece or earmold – the terminal conveyor of sound to the ear canal. Choice of earmold for a particular individual is perhaps the most subjective of all decisions made by clinicians in hearing aid fitting. It is not surprising, therefore, to find that present-day selection of earpieces is made on the basis of clinical experience with cases of similar hearing loss under the assumption that the needs are similar; sundry opinions of hearing aid wearers; or is left to the discretion of earmold manufacturers, who may or may not have valid information on the matter.

The well-known Harvard Report[1] on design objectives for hearing aids dealt briefly with the earmold. The major conclusion in this regard was that final tests in hearing aid selection cannot properly be made without an individually-fitted earpiece. This opinion was shared by Carhart,[2] who stressed that the custom-fitted earpiece which was to be worn with the instrument should be used in the selection process.

The salient points found in the literature concerning earmolds may be summarized as follows:

1. Individually-fitted earmolds must assure good retention and comfort, as well as a good acoustic seal.
2. Changes in width and length of the sound canal tend to affect the frequency response curve of a receiver-earmold system.
3. The conventional earmold tends to act as a finite low-pass filter, yet, certain modifications in its structure may render it a high-pass filter.
4. Earmolds fabricated from soft or hard plastic do not seem to affect the word identification ability of hearing-impaired subjects to any significant degree.
5. Sound pressure measurements in the auditory meatus, taken by means of a probe-microphone unit, compare reasonably well with those taken on a 2 cc coupler.

Information is lacking with respect to the effect of commonly used earmold types (e.g., belled, vented, cavernous), on the discrimination ability of hearing-

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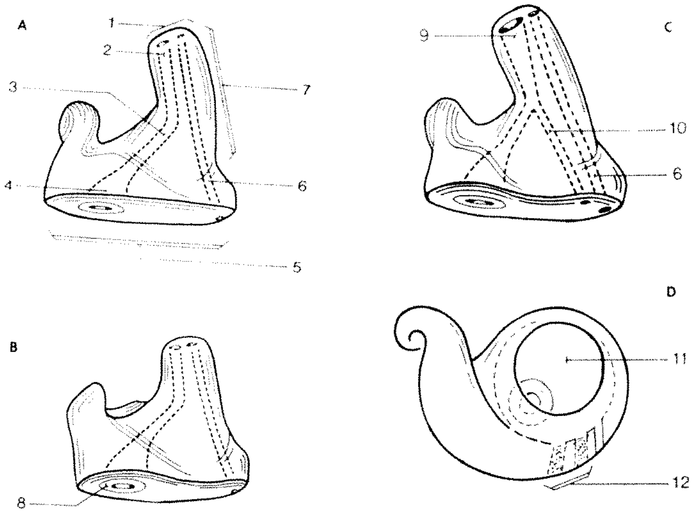

Fig. 1. A) Standard Long Earmold. 1, tip terminus; 2, medial port; 3, central sound canal; 4, external port; 5, base of the earmold; 6, probe-tube passageway; 7, earmold tip. B) Standard Short Earmold. 8, metal snapring. C) Belled Vented Earmold. 9, bell-shaped medial port; 10, vent. D) Cavernous Short Earmold. 11, air cavity; 12, vents plugged with cotton.

impaired subjects. The present study is an attempt to investigate the performance of selected earmolds, using standard speech discrimination tests, and to compare this performance with real-ear acoustic measures.

METHODS AND MATERIALS

Thirty-six adult male subjects with hearing impairment, determined by standard audiometric procedures, made up the experimental group. There were 19 hearing-aid wearers and 17 nonwearers; ages ranged from 25 to 56 years.

Criterion for Grouping. It was of clinical interest to assess how hearing-impaired subjects, having poor, good, or excellent discrimination ability, would perform with the experimental earmolds. Therefore three levels of discrimination ability were established a priori on the basis of the score on List "P" of Campbell's[3] redistribution of the W-22 recorded test.

A. Excellent Discrimination Ability — corresponding to scores of 88% or above.

B. Good Discrimination Ability — scores from 60 to 86%.

C. Poor Discrimination Ability — scores below 60%.

Twelve subjects were grouped in each category.

Experimental Earmolds. Figures 1 A, B, C, D depict the essential features of the earmolds used. In all cases, a passageway for the probe tube was drilled peripheral to the central sound canal. Other distinctive characteristics were:

1. Standard-long earmold — Usually called "Standard." It is the most commonly used earpiece, having a relatively long tip. The one used in this study had:

Central bore length = 30 mm, from metal ring to tip terminus.

Central bore diameter = 3.0 mm, at tip terminus (Fig. 1A).

2. Standard-short earmold — overall length reduced to 18 mm; central bore diameter 3.0 mm (Fig. 1B).

3. Belled-vented earmold — length and diameter of central bore were the same as in Figure 1; medial port enlarged into a bell shape; narrow vent provided for sound filtration (Fig. 1C).

4. Cavernous-short earmold — materially reduced in size (mass greatly reduced); cavernous central chamber; maximum diameter in medial port; two vents for sound filtration, plugged with cotton (Fig. 1D).

Probe Tube Technique. The procedure followed was essentially the same as that employed by Ewertsen et al[4] for sound pressure measurements in the external auditory meatus.

A B & K probe microphone was inserted into the special passageway in the earmolds. The probe tube fitted snugly and reached up to, but not beyond, the tip terminus.

All probe tube acoustic measures were taken on one human ear — an ear which had no abnormality in the external auditory meatus. Measurements of frequency response, harmonic distortion and intermodulation distortion[5] were made.

Test Messages. Campbell's[3] redistribution of the W-22 recorded monosyllabic word test and Fairbank's[6] test of phonemic differentiation, the "Rhyme Test," were used.

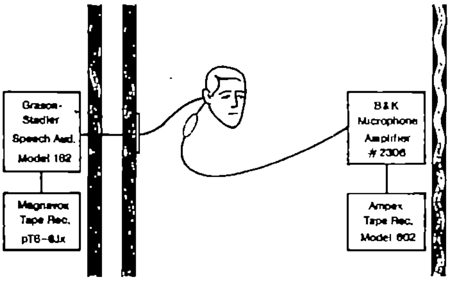
Grason-Stadler Speech Aud. Model 162
Magnavox Tape Rec. pT6-ℓJx
B & K Microphone Amplifier # 2306
Ampex Tape Rec. Model 602

Fig. 2. Block diagram of instrumentation for recording speech materials. B & K miniature receiver and probe microphone unit No. UA 0040 plus earmold.

Campbell's lists represent a revision of the CID Auditory Tests[7] with respect to average level of difficulty, a criterion which the CID W-22 lists do not rigorously meet, particularly for research needs.

Campbell assessed the relative difficulty of the CID lists from the percentage of erroneous responses made on each item by 40 hearing-impaired subjects. From the pooled data, he constructed eight lists of 25 words each, equated with respect to word difficulty.

Fairbanks' Rhyme Test is one in which auditory phonemic factors weigh heavily on the subject's response. Literacy demands are minimal. The test is of the completion type, short, easy to administer, and suitable for group presentation. Stimulus words are common monosyllabic words, which differ from one another only in the initial consonant phoneme, the rhyming portion (or "stem") in each row is spelled alike. The response sheet contains the word stems in their order of presentation, each stem preceded by a blank space. The subject is instructed to complete the spelling of the word by supplying the initial consonant, as he hears it.

The taped speech signal was fed through one channel of a Grason-Stadler Speech Audiometer to a circuit which led to the receiver-earmold unit, placed in the "real ear." The signal was then picked up by the probe-microphone ensemble, amplified, and rerecorded on magnetic tape (Fig. 2).

Listening Trials. Presentation of speech materials was conducted on an individual basis, using a twin-suite arrangement. As a preliminary step, a random order of presentation of the "treated" lists was arranged in order to counteract learning effects. The Rhyme Test was presented first; Campbell's lists last. A rest period was provided between tests to minimize the effects of fatigue.

DISCUSSION AND RESULTS

Responses in the Experimental Trials. Mean scores for all subjects on Campbell's test are given in Figure 3. It is evident that the average scores for two of the earmolds – the standard-long and the cavernous – were quite similar, while a substantial decrement in mean discrimination scores can be noted for the standard-short and belled-vented earmolds.

The histogram on the right presents the mean scores for the Rhyme Test. It is obvious that the mean performance of the 36 subjects was rather uniform for all earmolds. A comparison of the mean performance of Groups A, B, and C (excellent, good and poor discrimination ability) in all listening trials appears in Figure 4. The groups were consistent in their mean responses in Campbell's test, that is, the highest mean scores for all groups were achieved with the standard-long and cavernous earmolds; the lowest scores with the standard-short and belled-vented. Again the Rhyme Test was not differentiating inasmuch as the groups performed al-

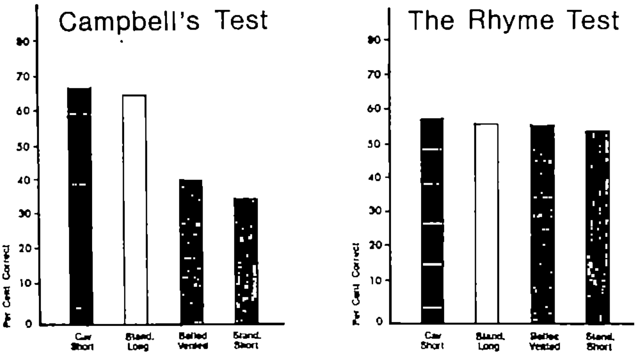

Fig. 3. Mean discrimination scores for Campbell's test and the Rhyme test on 36 hearing impaired subjects.

TABLE 1. AVERAGE PERCENT HARMONIC DISTORTION OF FOUR EARMOLD-RECEIVER SYSTEMS

	Earmolds			
Frequency in Hz	*Stnd-L*	*Belled-V*	*Stnd-Sh.*	*Cav.-Sh.*
500	2.8	1.2	3.1	1.9
700	2.3	2.9	1.7	1.1
900	4.0	3.0	1.2	1.7
Avg.	3.0	2.5	2.0	1.5

most equally with the four earmolds. These results are in agreement with those of Northern and Hattler[8] who also did not find a significant difference between earmolds using the Kruel et al[9] modification of the Rhyme Test. Our results were statistically significant for the Campbell lists but not for the Rhyme Test.

The fact that Campbell's lists differentiated between the earmolds while the Rhyme Test did not is evidence that the acoustic characteristics of the signal interfered more with the correct identification of monosyllabic words than with the identification of initial word phonemes. In other words, the distortion of the speech signal by the earmold was not as detrimental to phonemic identification as it was to word identification.

Electroacoustic Measures. Harmonic distortion in each earmold – B & K system, measured by the standard procedure for hearing aids, was averaged over 500, 700, and 900 Hz. As shown in Table 1 the harmonic distortion for all molds was below the 5.0% level – a level considered minimal in judging hearing aid characteristics. It is of interest to note that these harmonic distortion measures using the B & K amplifier were much lower than those reported by Northern and Hattler[8] who used a body-type hearing aid. Thus our intent to study the earmold effect rather than the hearing aid was achieved.

Neither harmonic nor intermodulation distortion proved useful in ranking the earmold-receiver systems. The criterion on which ranking was possible was the frequency response overall range as specified by the HAIC method.

Table 2 presents the frequency response of the earmold-receiver systems. It can be noted that the widest ranges were obtained with the standard-long

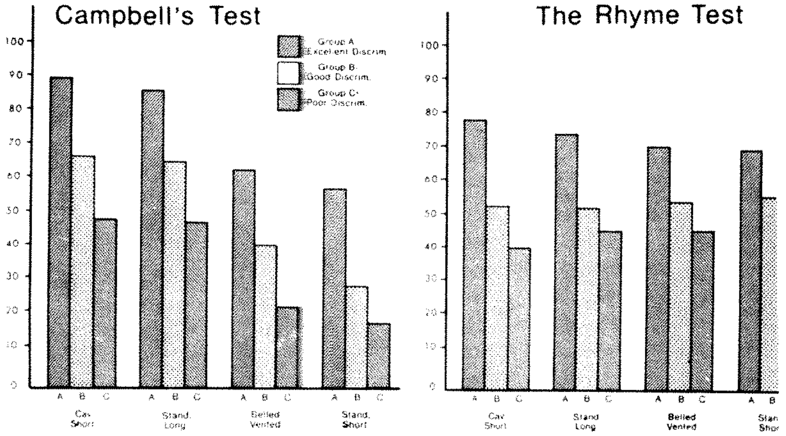

Fig. 4. Mean discrimination scores of group A, B, and C for two speech tests and four earmolds.

TABLE 2. RANKING OF EARMOLD-RECEIVER SYSTEMS BASED ON FREQUENCY RESPONSE OVERALL RANGE (HAIC METHOD)

Earmold Receiver System	*Frequency Range Hz*
(1) Standard-long	60-5000
(2) Cavernous-short	175-5250
(3) Belled-vented	100-3000
(4) Standard-short	275-3000

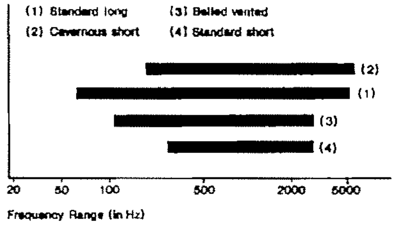

Fig. 5. Frequency range of earmold-receiver systems.

and cavernous earmolds while the narrowest ranges were obtained with the standard-short and belled-vented. Figure 5 presents a graphic version of these data. The results are in agreement with those of Olsen and Wilber[10] who reported that bandwidth was more important to intelligibility than either harmonic or intermodulation distortion.

Performance of Hearing-aid Users and Nonusers. It was of interest to see how the discrimination scores of the 19 hearing-aid users in the present study compared with the scores of the 17 nonusers. These groups were heterogeneous with regard to excellent, good, or poor discrimination ability, as operationally defined. Figure 6 is a graphical representation of these data. Substantial mean score differences are obvious in Campbell's test, pointing to differences in the earmolds, but such differences were not obtained with the Rhyme Test. The hearing-aid users obtained consistently better scores than the nonusers in all listening trials, but this was attributed to the group composition with respect to discrimination ability. The hearing-aid group had only three subjects with poor discrimination, while more than half of the subjects in the nonhearing aid group were in the "poor" category. However, the superiority of the cavernous and the standard earmolds over the short-standard and belled-vented was maintained.

Group Performance in "Treated" and "Untreated" Lists. Campbell's List "P," which served as the pretest for assigning subjects to levels of discrimination ability, represented "untreated" speech material, that is, presented through the speech audiometer only. Discrimination scores obtained with List "P" were regarded as the best estimate of discrimination for monosyllabic words (PB Max) for each subject. Word lists which were recorded through the earmold — B & K systems were designated as "treated" lists. A comparison between mean scores for treated and untreated lists was attempted in order to assess

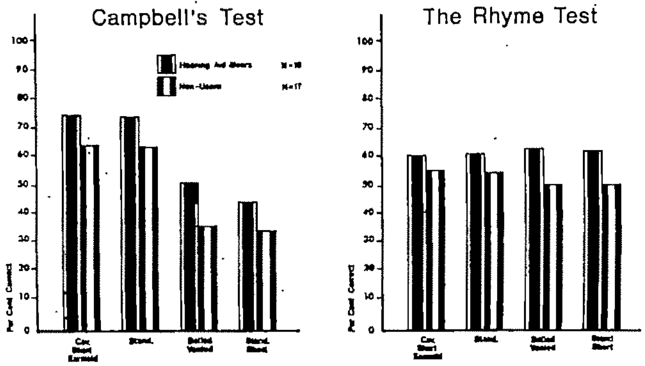

Fig. 6. Mean discrimination scores for hearing aid users and nonusers on four earmolds and two speech tests.

TABLE 3. MEAN DISCRIMINATION SCORES OF 35 SUBJECTS ON "TREATED" AND "UNTREATED" WORD LISTS

Groups	*"p"*	*Cav.*	*Stnd.-L.* *(In Percentage)*	*B-V*	*Stnd-Sh.*
A	95.30	89.16	86.83	63.33	58.66
B	67.00	66.00	64.66	40.00	29.33
C	44.00	47.33	46.66	21.00	18.33

the margin of approximation or separation of earmold performance to scores on List P. Table 3 presents a ranking of those observations. Inspection shows that an excellent approximation of scores obtained with the cavernous and standard-long earmold to the scores on List "P" occurred. This trend is evident in all groups. The mean for the belled-vented and standard-short earmolds separated considerably from the List "P" score. This pattern was observed from group to group.

CONCLUSIONS

The following conclusions can be stated from the results of this study:

1. Performance differences in earmolds of contrasting design can be assessed by discrimination scores with monosyllabic word lists of equal difficulty.

2. Among the physical measures taken of the earmold-receiver systems, frequency-response overall range (HAIC method) ranked the devices in agreement with group responses to a word identification task.

3. These data offer a basis for endorsement of the standard-long and cavernous-short earmold types over the belled-vented and standard-short types. The superiority of the first two earmolds was evident in each of the discrimination categories: excellent, good, and poor.

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MASTICATOR SPACE ABSCESS COMPLICATING REMOVAL OF SUSPENSION WIRES

CASE REPORT

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SUMMARY — Masticator space abscesses have been reported more frequently in recent years. They are usually secondary to extractions of the first and second mandibular molar teeth. The use of antibiotics has changed the presentation and clinical course of these abscesses, masking the symptoms and resulting in secondary infection by resistant organisms. Therefore, selection of appropriate antibiotics is important, but surgical intervention remains the cornerstone of treatment. Suspension wires are being used widely in the treatment of midface fractures. These wires may extend from the zygomatic arch or frontal bone through the masticator space into the oral cavity to attach to arch bars. A case of masticator space abscess resulting from the removal of suspension wires is reported, and the relevant literature is reviewed. Suggestions are made for preventing and treating this complication.

The incidence of deep neck infections has decreased since the discovery of antibiotics, but the classical signs and symptoms of these infections are often masked by antibiotic therapy.[1-2] In addition, these infections are now commonly caused by aerobic and anaerobic organisms that are resistant to penicillin. Therefore, diagnosis is often delayed, and treatment may be difficult.

Suspension wires are being used widely in the treatment of midface fractures. These wires may extend from the zygomatic arch or frontal bone through the masticator space into the oral cavity to attach to arch bars. They may be removed by reopening the skin incision over the frontal bone or zygoma, cutting the wire and pulling it down into the mouth from below. Using this technique, no contamination of the masticator space occurs from oral flora. Alternatively, the wire may be cut from its attachments to the arch bar and removed from above, using a cut-down or pull-out wire, or from below by grasping one end of the wire that has been attached to the arch bar. Using either of these latter two techniques, the surgeon risks contaminating the masticator space with organisms from the mouth that are carried by the wire along its track of removal.[3]

The masticator space contains the following structures: the temporalis, masseter, medial and lateral pterygoid muscles, the temporomandibular joint, the ramus of the mandible, the masticatory fat pad, branches of the maxillary division of the trigeminal nerve and branches of the internal maxillary artery.

The boundaries of the masticator space are formed by a continuation of the superficial layer of investing cervical fascia that passes from the neck to the inferior border of the mandible (Fig. 1). It attaches to the periosteum at the inferior border of the mandible and continues superiorly to cover the muscles of mastication that attach to the mandible. Laterally, this fascial layer covers the external surface of the masseter muscle and extends upward to attach to the zygomatic arch. From there, the fascia extends over the lateral surface of the temporalis muscle. This fascia lies medial to the parotid gland, facial nerve, parotid duct and buccal fat pad, which are not within the masticator space. The fascial layer cov-

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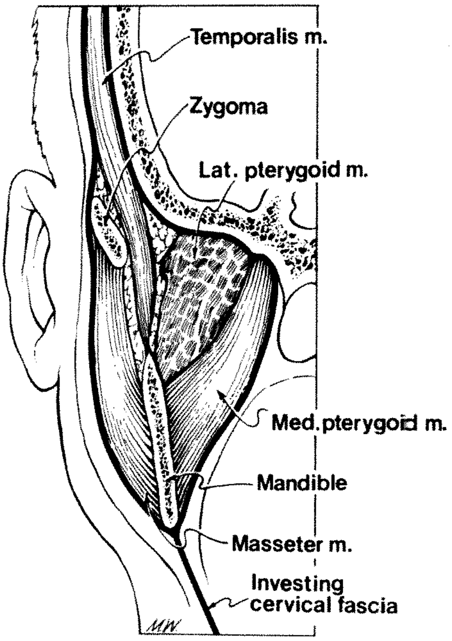

Fig. 1. Anatomy of the masticator space. Note the boundaries of the masticator space represented by the thick black line. The fascia that forms this boundary is a continuation of the superficial layer of investing cervical fascia. The structures contained within the space include the temporalis, lateral pterygoid, medial pterygoid and masseter muscles, mandible and zygoma.

ers the medial surface of the medial pterygoid muscle. Within this compartment, the fascial layer splits to envelop the medial and lateral pterygoid muscles, the mandible and the temporalis muscle. Therefore, several compartments exist within the masticator space. The compartment lateral to the mandible contains the masseter muscle and is commonly affected by masticator space infections and abscesses. The medial and lateral layers of fascia fuse anteriorly along the anterior border of the masseter and temporalis muscles and posteriorly along the ramus of the mandible and the temporalis muscle. Superiorly, a superficial temporal compartment lies between the temporalis muscle and the lateral layer of fascia, and a deep temporal compartment lies between the temporalis muscle and periosteum overlying the temporal bone.[4] Some authors consider the deep temporal compartment to be separate from the masticator space.[5] The firm attachment of the superficial layer of investing cervical fascia to the inferior border of the mandible separates the medial and lateral inferior compartments from each other and from the deep neck spaces below the level of the mandible. However, infection may spread from one compartment to the other by passing posteriorly around the ramus of the mandible or superiorly into the temporal compartments.

Although infections of the masticator space are usually secondary to odontogenic infection,[6] they may originate in the parotid space, the lateral pharyngeal space or from the injection of local anesthetics for inferior alveolar nerve blocks.[7] They may be contracted from *Actinomyces bovis* infection (lumpy jaw) of cattle.[8]

The mouth contains both aerobic and anaerobic organisms, including streptococci, staphylococci, pneumococci, lactobacilli, fusiform bacilli, *Klebsiella pneumoniae, Proteus vulgaris, Borrelia vincentii* and other spirochetes.[9] Various antiseptic mouthwashes, such as hydrogen peroxide,[10] hexachlorophene,[11] Cepacol®,[12] Listerine®[13] and iodine-containing solutions,[14] are effective in decreasing the concentration of oral flora.[9-14] Iodine-containing mouthwashes may prevent bacteremia following tooth extraction.[14]

Since masticator space infection usually follows molar tooth extractions or fracture, a history of dental extraction should be sought in the interview.[6] The most prominent symptoms of masticator space abscesses are trismus and severe pain and swelling in the area of the masticator space. The swelling may point intraorally or externally[6-8] and may drain spontaneously into the mouth or external auditory canal.[15] Intraoral drainage is performed if the abscess points intraorally.[7] External drainage, which is preferable if the abscess also points externally,[6] may be provided by a horizontal neck incision below the angle of the mandible. Dissection is carried through the periosteum to the bone of the mandible.[6,7] An abscess within the temporal compartment of the masticator space may be drained through a suprazygomatic incision. Drainage of both the temporal (superior) and the inferior compartments may be accomplished by passing through-and-through drains from the incision above the zygoma to the incision below the angle of the jaw.[6] Alternatively, a modified Blair incision has been recommended[8] and was used successfully in the case reported here.

CASE REPORT

A 20-year-old sailor sustained multiple injuries in an automobile accident on October 31, 1973. These injuries included left clavicular and left femoral bone fractures, a Le Fort II fracture of the midface, a nondisplaced nasoethmoid fracture with transient cerebrospinal rhinorrhea and mandibular fractures.

On November 8, 1973, his fractures were reduced. The mandibular and zygomatic fractures were fixed with interosseous wire, and the mandibular and midface fractures were supported with Erich arch bars and intermaxillary fixation. The upper arch bar was suspended from the right frontal bone and left zygomatic arch with the left suspension wire looped over the arch and the right suspension wire threaded through the frontozygomatic interosseous wire.

At the time of transfer to a second hospital, the patient's condition was stable, and his fractures were healing well. He was taking liquids by mouth and walking with crutches. Standard oral hygiene, including saline mouthwashes, was observed. His intermaxillary bands were replaced with wires.

Eight weeks after reduction and fixation of his facial fractures, the arch bars and suspension wires were removed. Surgery was performed under intravenous Valium® and local Xylocaine® with epinephrine. The surgeon's hands were scrubbed and gloved. To avoid distracting the healing right frontozygomatic fracture by pulling the suspension wire from below through the interosseous wire, an incision was made at the site of the old brow-incision. The wire was cut from above and removed from below. The brow-incision was performed in a sterile field prepared with Betadine®, but no intraoral topical preparation or prophylactic antibiotics were used. The left suspension wire, which was cut as high as possible in the mouth, was removed in the usual manner, from below by dragging the cut end of the suspension wire up through the masticator space, over the zygomatic arch and back through the masticator space into the mouth.

On the third postoperative day, the patient's temperature gradually increased to 38.3 C. Pain, tenderness and swelling developed over his left cheek and inferior eyelid. A diagnosis of cellulitis from oral flora secondary to removal of his suspension wires was made. Buccal mucosal culture revealed alpha *Streptococcus hemolyticus*. He was given penicillin intravenously, and warm compresses were administered. On January 8, 1974, an incision was made in the left temporal fossa. Five cc of yellow-white pus were drained from the superficial temporal compartment of the masticator space, and a Penrose drain was inserted. Gram's stain was unrevealing. Culture grew herellea. His antibiotics were changed to oxacillin and streptomycin. Initially, he responded well, but relief was only temporary. At this time, the pain, swelling and tenderness were associated with trismus. On January 14, oxacillin and streptomycin were discontinued. He was begun on gentamicin, 80 mg intramuscularly, every eight hours and clindamycin, 600 mg intravenously, every six hours. A modified Blair incision was made. Blunt dissection was used to enter an abscess lying on the periosteum of the lateral aspect of the mandibular ramus (Fig. 2). Drains were placed into the abscess. Anaerobic and aerobic cultures grew only *E. coli*. He rapidly became afebrile, and his swelling and trismus completely disappeared. The gentamicin was discontinued on January 28 and the clindamycin on February 4.

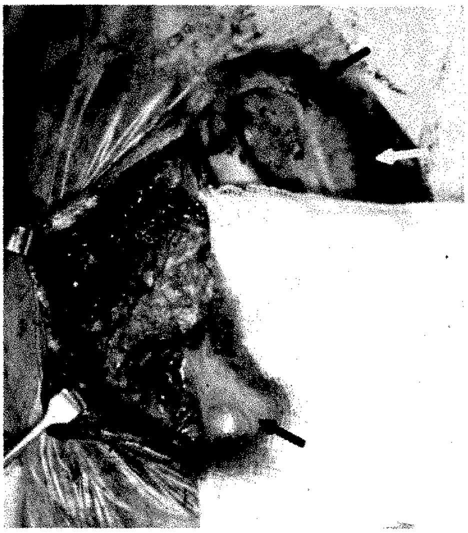

Fig. 2. Drainage of the left masticator space infection through a modified Blair incision. The double arrows point to the auricle. The single arrow points to the pus draining from the abscess.

DISCUSSION

Removal of suspension wires has not been reported previously as a cause of masticator space infection. In fact, this complication is quite rare but not insignificant.

Although Converse suggests the possibility of oral contamination of the masticator space from this procedure, he still recommends removal of the suspension wires from above, using pull-out wires.[3] This complication can be prevented by cutting the suspension wires through skin incisions superiorly and removing them from below without dragging the intraoral portion of the wire through the masticator space. If the suspension wire cannot be removed in this manner, the mouth should be rinsed with an antiseptic solution to decrease the concentration of the oral flora. The wire should then be cut as high as possible within the mouth.

When this complication does occur, it must be treated vigorously with antibiotics and, in the case of an abscess, with incision and drainage. The choice of antibiotics should be made on the basis of culture and sensitivity tests for both aerobic and anaerobic bacteria.

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XII WORLD CONGRESS OF OTORHINOLARYNGOLOGY

The XII World Congress of Otorhinolaryngology will be held June 21-26, 1981 in Budapest, Hungary. Preliminary communications, recommendations and suggestions, should be directed to Prof. Dr. L. Surján, President, XII World Congress of ORL, H-1389 Budapest, Pf: 112 Hungary.

Ann Otol 87:1978

DERMOID OF THE NASOPHARYNX

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SUMMARY — A case of a cystic polyp of the nasopharynx in a three-year-old Caucasian female is presented. Although cases of teratomas of the nasopharynx have been reported, our literature search revealed only one prior report of a hamartoma. To our knowledge, a lesion with these histological features occurring in the nasopharynx has not been previously reported.

A three-year-old Caucasian female was admitted to the University Hospitals on January 13, 1976, with rhinorrhea and persistent nasal obstruction. The parents noted frequent mucus drainage from both nasal passages and constant mouth breathing since six months of age. Physical examination revealed a firm, fixed, nodular mass completely filling the nasopharynx and visible inferior to the soft palate and uvula. A lateral radiograph of the neck outlined the mass in the nasopharynx. Routine blood studies, chest and sinus films, and a chloride sweat test for cystic fibrosis were within normal limits. Under general endotracheal anesthesia, the soft palate was retracted anteriorly, and a 4 x 3 cm mass arising from the posterior pharyngeal wall by a small pedicle was excised with minimal bleeding. The postoperative course was uneventful. An eight-month follow-up period has revealed no recurrence of the lesion, and the nasal obstruction has cleared.

PATHOLOGIC FINDINGS

The gross specimen weighed 3.2 gm and consisted of a firm, creamy-white lobulated mass (Fig. 1). On section, a small area of calcification was identified. Microscopic examination revealed a nonkeratinizing, squamous, epithelial-lined lesion. Dilated, invaginating, cystic channels lined by squamous epithelium were also present. Another field exhibited keratin inclusion cysts (Fig. 2). Many small vascular spaces with a chronic inflammatory infiltrate of lymphocytes and plasma cells beneath the epithelium were conspicuous. Occasional ducts lined by one or two layers of cuboidal epithelium and areas of squamous metaplasia with foci of metaplastic bone appeared.

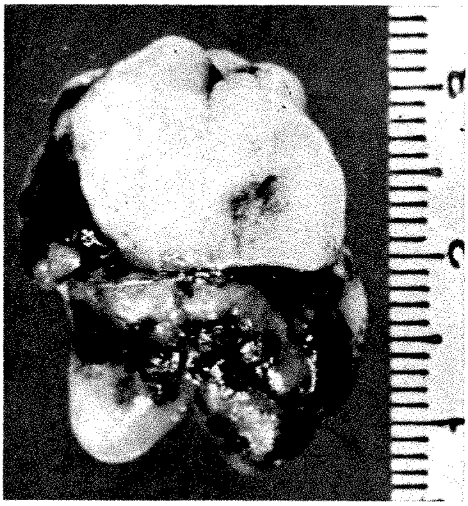

Fig. 1. Gross specimen showing firm lobulated tumor mass.

Ultrastructure studies revealed numerous blood vessels lined with normal-appearing endothelial cells. Fibrocytic cells with prominent collagen production and epithelial elements, most of which appeared to be of squamous cell type with conspicuous desmosomes, were also present (Fig. 3).

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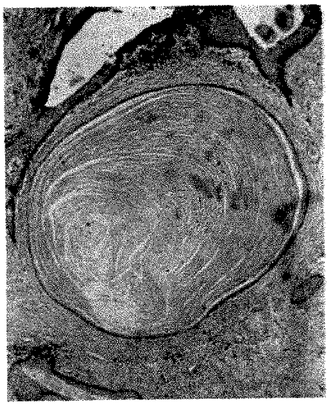

Fig. 2. Low power view of tumor showing connective tissue stroma and inclusion cyst filled with keratin. (H. & E., X40).

Examination of multiple sections failed to show other types of tissue to suggest a true teratoma.

DISCUSSION

To our knowledge, a lesion with the above histologic features occurring in the nasopharynx has not been previously reported. A lesion described as a seromucinous glandular hamartoma in the nasopharynx has been reported by Baillie and Batsakis.[1]

Teratomas of the nasopharynx, although infrequent, have been reported.[2,3] These tumors were classified by Calcaterra[3] into four types: a) dermoids, b) teratoids, c) true teratomas, and d) epignathi. Derivatives from all three germ layers that are well-differentiated must be present for the lesion to be classified as a true teratoma.[3] Serial sections through our specimen showed epithelial elements and metaplastic bone. Consequently, a diagnosis of a true teratoma could not be made.

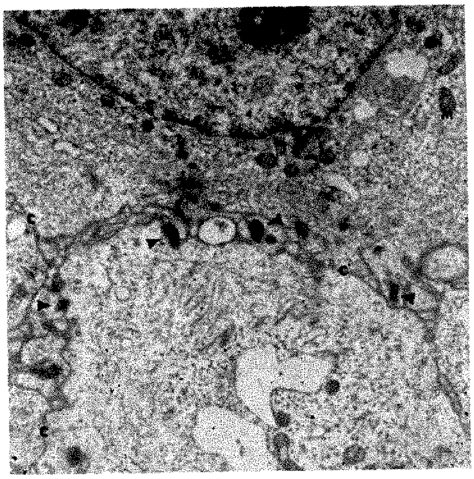

Fig. 3. Electron micrograph showing cells with conspicuous desmosomes (arrows). N - Nucleus. M - Mitochondria. C - Cell membranes. (X9400)

The association of nasal polyps with cystic fibrosis is well known.[2,4] This polyp can be called a dermoid, which is a form of teratoma, according to Calcaterra's classification.[3] Dermoids should have both epidermal and mesodermal germ layers. The presence of bone within the lesion qualifies this lesion as a dermoid. The terms hamartoma and dermoid are interchangeable in this case, the latter term being more commonly used.

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EFFECTS OF ADENOIDECTOMY

A CONTROLLED TWO-YEAR FOLLOW-UP

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SUMMARY — A prospective controlled study was made on the effect of adenoidectomy performed on 105 children. For various reasons, mainly severe long-standing nasal obstruction, 29 children were omitted from the study. The remaining 76 children were randomly divided into two groups, one adenoidectomy, and one control. Both groups were slightly reduced in number due to drop out. Thus 36 adenoidectomized children were followed during one year and 35 children during two years. The corresponding numbers for the children in the control group were 37 and 33. The incidence of common cold, purulent and serous otitis media and moderate nasal obstruction was compared in the two groups. A considerable reduction in the incidence of these variables was observed in both groups. The occurrence of moderate nasal obstruction was reduced more among the operated than among the unoperated children. The difference was only slightly significant during the first and not at all during the second year. Regarding the other variables, the differences were not significant, implying that adenoidectomy seems to have no effect on the incidence of common cold, serous and purulent otitis media.

Current textbooks of ear, nose and throat diseases recommend adenoidectomy as the treatment of choice in children with not only nasal obstruction but also with a history of recurrent upper airway infections, otitis media, serous otitis media and sinusitis. Relative indications are recurrent sore throats, rhinitis and even failure to thrive.[1-7] A more critical attitude towards the above mentioned indications can also be found.[8]

The emphasis with which the operation is recommended strikingly contrasts with the paucity of evidence of its beneficial effects. Proper knowledge of the effect of therapeutic procedures should be based either on controlled prospective studies or on well designed experiments. Few studies in the first category have been published.[9-13] Only one of these studies deals with the effect of adenoidectomy[10] whereas the others are concerned with the effect of the combined adenotonsillectomy operation (T and A). In a critical study of 29 papers on T and A recently published by Shaikh et al[14] only one, McKee,[9] reached as high as half the maximum score which could be reached for a good controlled study.

Bluestone et al[15] achieved interesting experimental results using the inflation-deflation method to evaluate tubal function before and after adenoidectomy in children with long-standing serous otitis media. They found that adenoidectomy gave favorable results only in cases where the Eustachian tube was not pliable. The conclusions that can be drawn from even the best studies seem to be contradictory, and the need for further prospective controlled studies has been strongly pointed out by Paradise[16,17] and by many other workers.[14,15]

In our opinion the effect of adenoidectomy on recurrent purulent and serous otitis media and frequent upper airway infections is not well documented. For this reason we found that the ethical problem of creating an unoperated control group could be regarded as negligible. The ethical problem was further reduced by the fact that when our new

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TABLE 1. REASONS FOR EXCLUDING 29 OUT OF 105 CHILDREN ADMITTED TO THE TRIAL

	No. of Patients
Cases of severe nasal obstruction	10
Operation performed in other hospital	5
Refused operation	4
Cases of recurring adenoids	2
Diabetes	1
Administrative mishaps	7
Total	29

department opened, our facilities for surgery were limited. Thus, it was not possible to operate upon all children who were referred to us for adenoidectomy. Furthermore, in Sweden, adenoidectomy is by tradition usually performed without a simultaneous tonsillectomy. Thus, we had the opportunity to perform a controlled prospective study on the effect of adenoidectomy. The investigation started in early spring 1974, and was continued throughout 1975 and 1976.

METHODS AND MATERIALS

Our patient material consisted of 105 children consecutively scheduled for adenoidectomy during the spring of 1974. All children were examined by members of our own staff before they were ultimately accepted as candidates for adenoidectomy according to generally accepted standards, such as recurrent serous and purulent otitis media, frequent upper airway infections and nasal obstruction.

All children were given a clinical examination by one of us (R-D) and then they received a number between 0-105 randomly acquired by casting of lots. Children with even numbers came to belong to the adenoidectomy group (A-group) and those with odd numbers to the control group (C-group). At this time the children had waited an average of four months from the time of referral.

Twenty-nine children were omitted for reasons shown in Table 1, leaving 76 children to participate in the investigation. Thirty-nine of them were younger than 5 years, 23 were in the age group 5-7 years and 14 in the age group 8-12 years. Thirty-seven were girls and 39 were boys. About one-third of the children were referred to us by ENT specialists, one-third came from children's welfare centers, and in the remaining third the referrals came from members of our own staff.

A detailed history for the preceding year was taken according to a special questionnaire, where a history of a period with increased nasal discharge and/or sore throat with or without increased body temperature was taken as a criterion for a positive diagnosis of common cold. Regarding purulent otitis media, a reported diagnosis by a physician qualified as one spell of otitis. An opaque drum with decreased mobility at the examination, or a history of hearing loss more than two months reported by the parents, or a reported diagnosis of serous otitis media made by a physician was regarded as serous otitis media. A diagnosis of tonsillitis made by a physician was required for the notation of a spell of tonsillitis. Only more obvious forms of allergy such as asthma and eczema were accepted as criteria for being an allergic child.

For children in the age group younger than five years it was also noted whether or not they attended any kind of group care. All the others were school children.

The clinical examination consisted of a routine ENT examination, x-ray of the epipharynx, pure tone audiogram (age so permitting) and a bacterial culture from the nasopharynx. The eardrums were examined with the pneumatic otoscope in the younger and with the microscope in the older children. Adenoidectomy was performed under short anesthesia in 37 children. The patient's head was tilted and the adenoid was removed by means of a Beckmann ringknife. All children in the A-group had their ears examined under the microscope. When signs of otitis were present, a myringotomy was performed. A myringostomy tube was inserted if the secretion was tenacious. Serous otitis media was treated in the same way in the C-group.

The one-year follow-up consisted of at least two examinations taking place 6 and 12 months after the start of the trial. Many of the children were also examined after three and nine months. In the two-year follow-up the children were examined at the same intervals as described above and also after 24 months. (The two groups consisted mainly of the same children but the drop out continuously reduced the number of children participating. To avoid an unnecessary depletion of the one-year material we chose to divide the children in a one-year and a two-year group.) At every checkup a routine ENT examination was carried out and the incidence of the studied variables was observed. The number of colds in the elapsed period was recorded and given as number per years. A reduction in number of more than two periods of illness was regarded as an improvement and an increase of two or more as a deterioration. The same criteria were used to classify changes in the frequency of purulent otitis media. Serous otitis media was recorded as existing or nonexisting according either to history and or status at the time of checkup. A change from existing to nonexisting serous otitis media was regarded as an improvement, a change from nonexisting to existing was regarded as deterioration. Nasal obstruction was given as frequent or infrequent. A change from frequent to infrequent was regarded as

TABLE 2. INCIDENCE OF VARIOUS DISEASES IN NUMBERS PER YEAR PRIOR TO ONSET OF THE STUDY

		A-Group *($N = 37$)*	*C-Group* *($N = 39$)*
Common colds	0-1	0	1
	2-3	7	8
	4-6	9	8
	7	21	22
Purulent otitis media	0-1	19	17
	2-3	8	8
	4-6	5	7
	7	5	7
Serous otitis media		12	18
Tonsillitis		5	4
Nasal obstruction		27	23

an improvement, a change in the reverse direction as a deterioration.

To avoid unnecessary irradiation, x-ray examination was not repeated. At the time of the two-year checkup the children's ears were examined by microscope and pure tone audiograms were taken in all but two children in each group. Bacterial cultures from the nasopharynx were taken only at the two-year checkup. Unfortunately, four children could be reached only by telephone. In only one child was this procedure accepted more than one time. Thus 2 of the 36 children in the A-group and none in the C-group were telephone interviewed at the one-year checkup. At the two-year checkup two in the A-group and one in the C-group were examined in this way.

The hypothesis that the probability of becoming better is greater in the A-group than in the C-group was tested for significance by means of a one-sided test based on the normal distribution.[18]

At the beginning of the trial the studied variables randomly occurred in the two groups as follows: the distribution of children under the age of 5 attending group care (including those in family care and kindergarten) was nine in the A-group and seven in the C-group. Table 2 shows comparisons between the A-group and C-group in regard to histories of common colds, purulent otitis media, serous otitis media, tonsillitis and nasal obstruction.

Pathogenic bacteria (*Diplococcus pneumoniae, Hemophilus influenzae, Streptococcus hemolyticus, Staphylococcus aureus* and *Branhamella catarrhalis*) were found in 17 children in both the A- and C-group. There were six allergic children in the A-group and four in the C-group. X-ray examination disclosed a considerable enlargement of the soft tissue of the nasopharynx in 31 children in the A-group and 29 in the C-group. Four children in the A-group and five children in the C-group showed a moderate enlargement. The parents of seven children did not consent to x-ray examination. A moderate threshold elevation in the audiograms was observed in three children in the A-group and in one child in the C-group. Nineteen children had no pure tone audiograms taken.

RESULTS

Neither the adenoidectomies, nor the myringotomies were complicated by surgical or anesthesiological mishaps.

The number of dropouts during the first year was three, and they were discharged from the study; two came from the A-group and one from the C-group, a reduction to 36 and 37 children, respectively.

During the second year the number of dropouts was one from the A- and four from the C-group. Two children from the C-group were adenoidectomized because of severe nasal obstruction and thus were excluded. The rest of the children dropped out because their families moved out of the area from which we draw our patients.

Table 3 shows the details of outcome with respect to common colds, purulent and serous otitis media, and nasal obstruction. Neither at the one-year, nor at the two-year checkup could any significant difference of improvement between the two groups be detected with respect to common colds, purulent otitis media, or serous otitis media.

At the one-year checkup three children in the A-group and one in the C-group still had tympanostomy tubes. Only one child in the C-group had it at the two-year checkup. At the time of the two-year follow-up 31 children in the A-group and 32 children in the C-group had a normal pure tone audiogram, whereas 2 and 1, respectively, had a moderate hearing impairment. No audiometry was performed in two children in the A-group and in one child in the C-group.

With regard to nasal obstruction, at the time of one-year checkup the improvement rate was higher in the A-group than in the C-group on the 5% level ($P = 0.04$), but after two years no difference could be detected ($P = 0.24$).

Prior to the start of the trial five and

TABLE 3. CHANGE IN FREQUENCY OF COMMON COLDS AND PURULENT OTITIS MEDIA AND IN OCCURRENCE OF SEROUS OTITIS MEDIA AND NASAL OBSTRUCTION COMPARED TO THE INITIAL STATE

		One-Year Follow-Up		*Two-Year Follow-Up*	
		A	*C*	*A*	*C*
Common colds	Better	27	27	27	29
	Unchanged	9	8	8	4
	Deteriorated	0	2	0	0
Total no. of patients		36	37	35	33
Purulent otitis media	Better	17	18	16	17
	Unchanged	19	19	19	16
	Deteriorated	0	0	0	0
Total no. of patients		36	37	35	33
Serous otitis media	Better	7	11	11	10
	Unchanged	26	25	20	21
	Deteriorated	3	1	4	2
Total no. of patients		36	37	35	33
Nasal obstruction	Better	22	15	22	18
	Unchanged	11	16	11	14
	Deteriorated	3	6	2	1
Total no. of patients		36	37	35	33

four children in the A- and C-group suffered from one or more attacks of tonsillitis. At the time of the two-year follow-up two and three children were improved, three and one were unchanged and three and none had deteriorated in the A- and C-group respectively.

Table 4 shows the occurrence of positive cultures for various bacteria from the nasopharynx at the start and the end of the study. In the A-group five patients with *D. pneumoniae* were found compared to ten in the C-group (Table 4). The difference is significant at the 5% level.

DISCUSSION

In his critical review of the literature concerning T and A, Paradise[16] outlined "the ideal investigation." Stimulated by this but also well aware of our limited economical and personnel resources, we designed our prospective investigation. An obvious limitation in our study apart from the relatively small number of children is the lack of

TABLE 4. CULTURE FROM NASOPHARYNX

	At Time of Onset of the Study		*At Time of 2-Year Follow-Up*	
	A-Group	*C-Group*	*A-Group*	*C-Group*
S. aureus	3	3	2	3
D. pneumoniae	9	9	5	10
H. influenzae	4	4	4	2
N. catarrhalis	0	0	2	1
S. hemolyticus	1	1	5	4
Total no. of patients with positive culture	16	17	18	20
No growth	16	17	14	9
No culture	4	3	3	4
Total no. of patients	36	37	35	33

a real control group of children from a healthy population.

Although this study is planned as a prospective one, data concerning frequency of illnesses were obtained retrospectively by interviews with the parents, which is often regarded as a disadvantage. However, Strangert[19] found the prospective and the retrospective methods equally efficient for collecting data regarding incidence of infections in day-care-center children. Furthermore, the retrospective method of collecting data must be regarded as unbiased at least for the period consisting of the year before the trial started. In the following two years we were naturally aware of whether the children belonged to the A- or C-group, making the method less unbiased.

Huddinge ENT clinic is the main clinic in the area. The physicians are salaried and have no vested interest in the outcome, a fact which might be of importance.[14]

It is always difficult to assess whether the incidence of common colds is increased or not but more than seven spells per year might be regarded as pathological.[20,21] Brownlee, quoted and modified by Howie,[22] found that 416 out of 651 children had less than four episodes of otitis media up to school start. It thus seems reasonable to regard more than four episodes per year of purulent otitis media as an increased incidence. Serous otitis media is also difficult to diagnose and the incidence of a positive diagnosis varies with the diagnostic tool from just a few percent up to 13.5% in a material of school children.[23] The rare occurrence of elevated tone-threshold does not contradict the fairly high incidence of serous otitis media.[24] Thirty out of 76 children certainly indicates an increased morbidity of serous otitis media. Taken altogether, the studied variables occur at an increased rate with a moderately even distribution between A- and C-group.

We found it reasonable to operate on children with severe and long-standing nasal obstruction, when it reached levels where the child's night sleep was badly disturbed, even if cor pulmonale was not found.[25] For this reason we refrain from statements on the effect of adenoidectomy in children with severe and long-standing nasal obstruction. The incidence of bacterial infections, mainly exudative tonsillitis, was low, hence no conclusions were attempted regarding the effect of adenoidectomy on this disease.

Our results in a relatively small number of individuals suggest that the treatment seems to have little effect on the incidence of these conditions. Concerning nasal obstruction, the difference after one year is significant on a level of 5%, but after two years the difference is no longer significant. This indicates that the treatment has a short-term effect on the frequency of this condition. It remains an open question as to whether it is worth operating on a child for such a moderate gain.

We have found an overall improvement regarding the frequency of common colds and otitis media in the children in both the adenoidectomy and control groups. This is in agreement with the findings of other workers[12,20-22] and probably reflects the natural history of these diseases.

As discussed, the diagnosis of serous otitis media is difficult. In this study we were mainly interested in the chronic cases. For this reason we would not limit the positive diagnosis to the findings in a few samples in the form of the checkup examinations but also included reports from the parents of periods of long-standing hearing loss. We are aware that our criteria for the diagnosis of serous otitis media are crude. For this reason we refrain from a more detailed presentation of our therapeutical results. Still, we believe that our methods grossly work in the same way in both groups and a decrease in the rate of serous otitis media similar in both groups suggests that adenoidectomy might not be efficacious in the treatment of this disease. This fact is supported by another study by Schiratzki* who reviewed 177 children with serous otitis media. In that study 98 children of 177 only needed one myringotomy and 79 children needed more than one such operation. The adenoidectomy rate was around 50% in both groups, implying that the adenoidectomy had no effect on the outcome of the disease. In 15 children the otitis was regarded as especially troublesome. Of these children ten were adenoidectomized with no apparent effect.

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*Schiratzki H: Unpublished data.

We have no explanation for the higher rate of occurrence of *D. pneumoniae* in the C-group than in the A-group at present. Even if the microflora in the nasopharynx can be reduced by means of adenoidectomy, it does not necessarily mean that the child's state of health improves. The children in our C-group suffered from very few infections.

It seems highly unlikely that infections which have been studied in this material can be due to serious immunological defects. On the contrary, otitis-prone children have been shown to have elevated levels of IgG, IgM and IgA in serum.[26] It is still an open question whether the removal of lymphatic tissue in the pharynx is beneficial or detrimental. A serological study of antibody levels to several childhood respiratory viruses and bacteria indicated that T and A did not significantly reduce antibody levels present before surgery.[27] On the other hand, investigations by Ogra[28] indicated that specific nasopharyngeal immunity to poliovirus could be altered by T and A.

Recent investigations have shown that adenoid lymphocytes are not identical to those found in the spleen and blood[29] and that they can be stimulated to antibody secretion by heat-killed bacteria such as *H. influenzae*. The adenoid seems thus to play some part in the development of immunity against infection in the upper respiratory tract.

Even if the role of adenoid tissue in the immune response is not finally settled, uncritical removal of such an organ can obviously not be recommended. Moreover, although surgical complications in adenoidectomy are lower than in T and A[10] they are not negligible. Thus a trained anesthesiologist is today an absolute requirement not only to make the adenoidectomy as safe as possible, but also to avoid unwanted psychological effects. Adenoidectomy is today a time-consuming and rather expensive procedure.[30]

This study suggests a view critical of adenoidectomy as treatment of frequent common colds, purulent and serous otitis media, and moderate nasal obstruction.

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AMERICAN SOCIETY FOR HEAD AND NECK SURGERY

The Twentieth Annual Meeting of the American Society for Head and Neck Surgery will be held in conjunction with the Society for Head and Neck Surgeons in Toronto, May 28-31, 1978 at the Harbor Castle Hotel. For further information write: Jerome C. Goldstein, MD, Secretary, American Society for Head and Neck Surgery, Division of Otolaryngology, Albany Medical College, Albany, NY 12208.

Ann Otol 87:1978

PERFORMANCE OF TESTS AND INTERPRETATION OF RESULTS

SUBMANDIBULAR SALIVARY FLOW TEST IN FACIAL PARALYSIS

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The submandibular salivary flow test, first introduced by Magielski and Blatt,[1] is useful in evaluating patients with facial paralysis.[2]

MATERIALS

The equipment used to perform a salivary flow test includes the Wilder short-taper blunt tip, medium-taper medium tip, and long-taper fine tip, and the Ruedemann short, delicate, needle-type dilators. These can be purchased from the Storz Surgical Intrument Company and they are numbered E-4360, E-4361, E-4362, and E-4366, respectively. In addition, I use No. 50 polyethylene tubing and the obturator that fits into the No. 5 suction tip, lemon juice, a piece of cotton, 1% Xylocaine®, and a TB syringe with a fine needle (Fig. 1).

TECHNIQUE

The patient is informed of the procedure and its purpose. Approximately 0.5 cc of 1% Xylocaine® is injected submucosally, where the two plica sublinguali folds come together (Fig. 2A). This will raise the puncta, making them stand out, as well as anesthetizing them and making the procedure painless. Finding the puncta and cannulating the ducts is greatly aided by using the binocular operating microscope. The opening is found by drying the punctum with compressed air and then looking for the bead of saliva at the end of the punctum. Once this bead of saliva is noted, the Wilder long taper fine tip dilator is gently placed into the opening (Fig. 2B). By twirling and advancing the dilator, the meatus is enlarged. Once this is done, the meatus is progressively dilated with increasingly larger dilators used in sequence. The opposite side is done in the same way.

Following dilation of the duct, the obturator from the No. 5 suction tube is threaded through a piece of No. 50 polyethylene tubing which has been cut to be three quarters of the length of the obturator. The obturator extending out of the distal end of the polyethylene tube in inserted about 5 mm into the punctum and then the polyethylene tube is twirled off of the obturator into the duct (Fig. 2C). Following this, the obturator is removed. If the tube does not enter easily, the tubing is probably kinked or has caught on a mucosal fold. The other possibility is that a false tract has been formed; for this reason, great care must be taken in order to be sure that the tube is in the duct as indicated by a flow of saliva from the polyethylene tube. The tubes are crossed, so that the tube entering the right side comes out of the left corner of the mouth, and the one in the left side comes out on the right side of the mouth (Fig. 2D). Crossing the tubes prevents kinking and provides for the free flow of saliva.

Once the tubes have been placed, a small piece of cotton saturated with lemon juice is placed in the oral cavity. Closed lips hold the tubes in place and drops of saliva from the tubes are counted simultaneously on each side, comparing one side to the other over a 60-second period, providing that there is a total of more than 20 drops over that period of time. If fewer than 20

From the Pittsburgh Ear, Nose and Throat Associates, Pittsburgh, Pennsylvania.

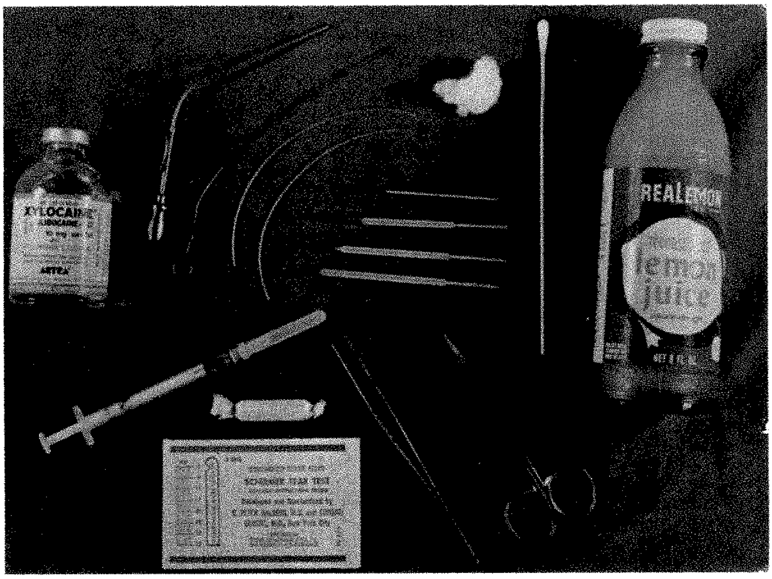

Figure 1.

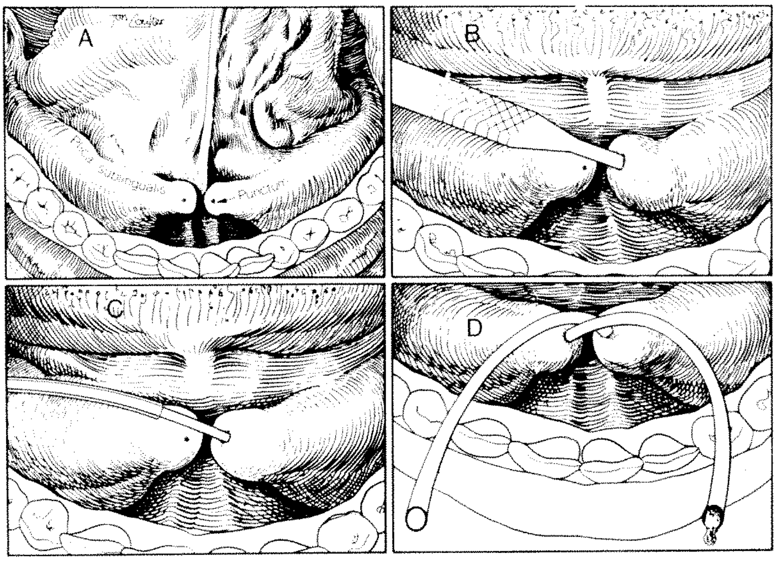

Figure 2.

drops are noted, then the time period is prolonged until a total of 20 drops for both sides is accumulated. The count is repeated three times. This allows for a statistically significant difference and eliminates error in interpretation of the results.

INTERPRETATION

The results of the salivary flow test are expressed as a percentage obtained by dividing the number of drops of saliva on the involved side by the number of drops from the normal side and multiplying this result by 100. A flow less than 70% is considered abnormal.

We have found that a linear relationship exists between the amount of flow and the incidence of denervation of the facial nerve: when the salivary flow is 25% or less, 90% of the patients develop denervation; when the salivary flow is between 50 and 26%, approximately half of the patients will develop denervation; and when the flow is between 70 and 50% of normal, the incidence of denervation is about 30%. Less than 10% of patients will develop denervation with normal salivary flow.

It is important to realize that the salivary flow is prognostically valuable only in the first few days following the onset of Bell's palsy, since during this period the percutaneous electrical test is still normal. Once there is a decreased response to maximal stimulation on the involved side compared to the normal side, one can predict with 80% accuracy that the patient will develop denervation regardless of the results of the salivary flow determination.[2]

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CLINICAL NEUROTOLOGY

The sixth continuing education course in Clinical Neurotology will be held October 16-19, 1978 at the Illinois Eye and Ear Infirmary, University of Illinois Abraham Lincoln School of Medicine. Inquiries to: Neurotology Section, Department of Otolaryngology, University of Illinois Eye and Ear Infirmary, 1855 West Taylor Street, Chicago, IL 60612.

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AMERICAN DIOPTER AND DECIBEL SOCIETY

Nationally known speakers in Ophthalmology, Otolaryngology and Allergy will be featured at the next meeting of the American Diopter and Decibel Society to be held April 2-8, 1978 in Scottsdale, Arizona. Inquire: E. A. Rittenhouse, MD, Executive Director, 522 Walnut Street, McKeesport, PA 15132.

Ann Otol 87:1978

REFLECTIONS OF AN OTOLARYNGOLOGIST

A SIGNIFICANT OCCASION FOR OTOLARYNGOLOGY

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Houston, Texas was the site of a very significant event during the first weekend of December 1977, the dedication of the Institute of Otorhinolaryngology and Communicative Disorders of the Neurosensory Center of Houston. Its completion represented the culmination of a long-held dream conceived by a group of forward-looking individuals in the Houston community. Two aspects of the Center are particularly unique and should be of interest to all of Otolaryngology. These concern first, its composition, and second, how support for its establishment was achieved.

To describe the organizational setup in detail is not within the scope of this article. Suffice to say, the Center is administratively related to the Baylor College of Medicine and the Methodist Hospital of Houston, a primary affiliated teaching hospital. Three clinical departments of the College of Medicine and the Methodist Hospital (Neurology, Ophthalmology, and Otolaryngology) have joined together in establishing the Neurosensory Center. They have pooled their resources to provide a site where patient care, educational, and research functions can be coordinated geographically not only within each discipline, but also among the three disciplines. Shared clinical facilities such as patient beds, operating rooms, intensive care units, laboratories, radiology, etc, should assure close clinical collaboration as well as efficient utilization. Separate, but immediately adjacent, research areas should likewise promote a continuing exchange of ideas and sharing of skills, techniques, and personnel. The proximity of the laboratory to the bedside and the close relationship of researchers and clinicians should further facilitate the translation of research findings into clinical applications within the neurosciences.

The marshalling of the support required to bring such a Center into being deserves a brief comment. The unique aspect is that support was generated almost entirely from private funds and from within the Houston community. With the experience of the past two decades fresh before us, when most health care facilities derived a significant degree of funding support from government sources, such an achievement is especially noteworthy. Hopefully it will give encouragement to others, for it appears that competition for government funds will become increasingly intense in the immediate future.

Some may raise questions about the concept of Otolaryngology in a Neurosensory Center, or the separation of the clinical otolaryngological facilities from the general hospital. Such questions are appropriate, but attempts at answering them should be deferred for yet awhile. On one side there may be those who feel this is a step backward. After all, they will say, isn't this just the opposite direction of what was considered progress ten years ago when Ophthalmology left the National Institute of Neurological Diseases and Blindness to become the National Eye Institute, and what is under way at present with the division of the American Academy of Ophthalmology and Otolaryngology into two separate organizations? Opposed to these views will be individuals who cite the growth during the past decade of the Society for Neuroscience, a vital and expanding group, and the active part played in this organization by researchers in audition and vision. The gradual disappearance of many of the separate eye and ear hospitals in this country during the past half century with incorporation of Otolaryngology into the general hospital was generally described as progress. However, many advantages of a separate facility can still be cited, such as the high quality of skill in personnel who are responsible only in a specific area. Only time and enough experience to provide honest and objective judgment can answer these questions.

Finally, it is obvious when one sees the high quality of what has been achieved in planning, building, and staffing the Neurosensory Center that the efforts and energies of many dedicated individuals have been involved. The name of one individual in the area of Otolaryngology does continually appear and should be recognized – Dr. Bobby Alford. We all owe Dr. Alford our thanks for his leadership in providing a facility of the highest quality as Otolaryngology's part of this innovative multidisciplinary venture. I am sure we all look forward to further benefits for otolaryngologic patients from its future growth and development.

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POSTGRADUATE COURSE ON HEAD AND NECK TUMORS

The National Cancer Institute of Milan and the Italian League Against Cancer, Milan Section, will organize a Postgraduate Course on head and neck tumors June 19-23, 1978. For further information write: Dr. Mario De Lena, Secretary, Ufficio Attività Didattiche, Instituto Nazionale Tumori, Via G. Venezian 1, 20133 Milano (Italy).

Ann Otol 87:1978

ENG OF THE MONTH

DILANTIN® SUPPRESSION

RICHARD W. BABIN, MD
IOWA CITY, IOWA

CASE REPORT

A 26-year-old Caucasian female epileptic was referred to University Hospital for a five week period of progressive disequilibrium which had become incapacitating. She had been on 300 mg of Dilantin® daily for several years. Two months prior to her presentation following a grand mal seizure, her dosage was increased to 400 mg daily. Her disequilibrium was described as waves of light-headedness and unsteadiness lasting several hours at a time. These spells were unassociated with hypacusis, tinnitus, true vertigo or headaches. Two days prior to her presentation, she fell during a severe episode lacerating her lip and chin. She did not lose consciousness and did not have a seizure at this time. There was no past history of head trauma, ear infections, or ototoxic drugs.

On presentation, the patient appeared quite unsteady, unable to maintain herself in an upright position in a wheelchair. She frequently closed her eyes and her head bobbed almost constantly. She could ambulate only with assistance and had an unsteady widebased gait. There was no tendency to fall in any given direction. Examination revealed ecchymosis and abrasions of her lip and chin. Tympanic membranes were normal, Weber was midline and air conduction was greater than bone conduction with 256 Hz, 512 and 1024 forks. Pupils were equal and external ocular motion was intact. There was end-gaze nystagmus without true spontaneous nystagmus and there was no rotatory or vertical component. Cranial nerves were intact, and rapid, repetitive motions were accurate but there was past-pointing with both hands. Deep tendon reflexes were brisk and symmetric. The remainder of the physical examination was normal.

Audiometric examination revealed a speech reception threshold of 10 dB bilaterally with normal discrimination scores. Tympanogram was normal except for absent bilateral acoustic reflexes at 500 and 1000 Hz. An ENG revealed mild calibration overshoot and no evidence of spontaneous, latent or positional nystagmus. The patient had almost no response in either ear to 5, 10 and 20 cc ice water irrigations (Fig. 1A). Serum Dilantin® levels were reported as 48 μg/ml (twice the maximum therapeutic level).

The patient was admitted to the Neurology service and her Dilantin® withheld. By the third hospital day, her serum Dilantin® level was 35 μg/ml (toxic) and she was still markedly ataxic and unsteady. During this time, spontaneous vertical nystagmus was often seen. Over the following two days, her level dropped to 20 μg/ml with resolution of her symptoms except for some mild nausea. The patient was restarted on Dilantin® 200 mg daily and maintained therapeutic blood levels. Workup revealed an abnormal EEG but no evidence of brain tumor. A repeat ENG at the time of discharge revealed brisk bilateral symmetric responses to 5 cc ice water (Fig. 1B).

From the Department of Otolaryngology and Maxillofacial Surgery, University of Iowa, Iowa City, Iowa.

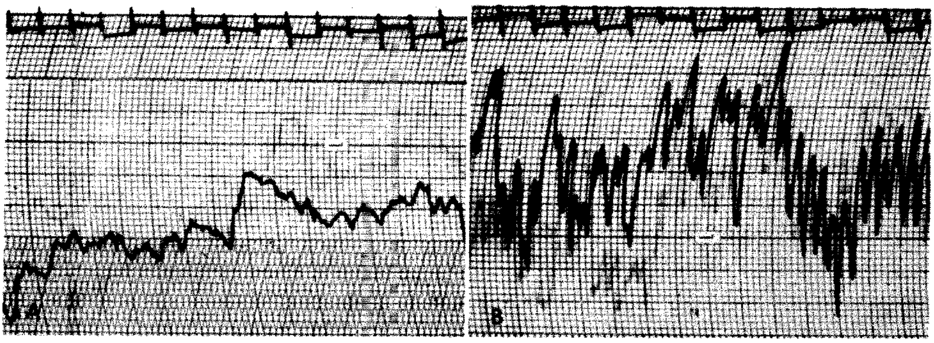


Fig. 1A) Response of patient to 20 cc irrigation of the left ear while there were toxic Dilantin® blood levels. B) Response of patient to 5 cc irrigation of ice water in left ear while there were therapeutic Dilantin® blood levels.

DISCUSSION

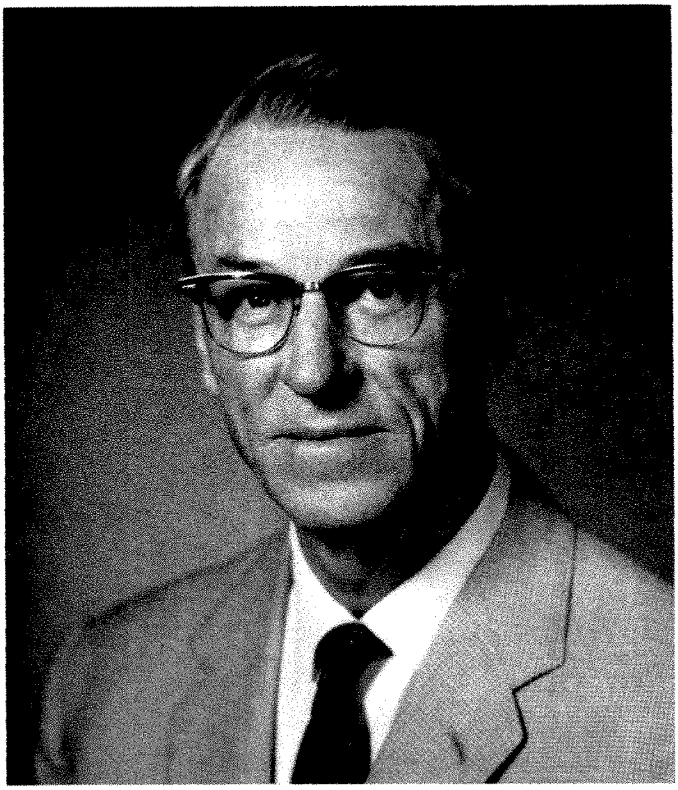
Dilantin® (phenytoin) is an anticonvulsant drug closely related to the barbiturates but without their generalized CNS depressant activity. Dilantin® reduces posttetanic potentiation of synaptic transmission, stabilizes cortical areas adjacent to seizure foci and reduces brain stem center activity. Its mechanism of action is presumably a facilitation of the sodium pump of the neural membrane. Dilantin® is metabolized by the liver and excreted in the bile. The serum half-life is 22 hours. This may be prolonged by liver disease or competitive inhibition by other drugs. Neither of these mechanisms can be implicated in the prolonged serum levels in our patient. Dilantin® toxicity most commonly presents just as our patient did with cerebellar ataxia, nystagmus and slurred speech. Less common CNS manifestations include agitation, insomnia, muscle twitching and headache. Suppression of vestibular function has not specifically been reported.

COMMENT

The absence of true vertigo (the hallucination of motion), normal hearing in the face of absent vestibular responses, absence of vegetative symptoms despite incapacitation and the eventual vertical nystagmus all suggested a central vestibular reflex arc disruption. The classic ataxia, calibration overshoot and past-pointing suggested cerebellar involvement.

The importance of a careful drug history in the workup of a "dizzy" patient must be emphasized. As in this case, the symptomatology may be the result of the pharmacologic or toxic effects of a current drug or damage done by an agent used in the past. Also important, however, is the knowledge of any current agent which might interfere with the proper evaluation of the oculovestibular reflex arc. Apparently Dilantin®, at least at toxic levels, also falls into this category.

Reprints — Richard W. Babin, MD, Assistant Professor, Department of Otolaryngology and Maxillofacial Surgery, University of Iowa Hospitals, Iowa City, IA 52242.



ANDERSON C. HILDING, MD, PhD

1892-1977

Anderson Hilding was born on June 29, 1892, and died December 5, 1977, at the age of 85 years. He was a man beloved by young and old alike. He was a kind and seemingly ageless man vitally interested in young people and their activities. Doctor Hilding had a good sense of humor, listened more than he spoke, taught by questioning and not by lecturing, admonished by example and not by scolding, and showed his love with deeds and not with words. His list of achievements stretched over 60 years bringing worldwide recognition and numerous awards, any one of which would be a great honor. An outstanding physician and an unusually gifted surgeon, his skills brought help to countless grateful patients.

Doctor Hilding graduated from the University of Minnesota Medical School in 1919. Four years of medical practice in Duluth were followed by a year of study in Vienna and a return to the University of Minnesota where he was granted a PhD in pathology; it was during these years that he conducted pioneering research on the role of the kidney in the regulation of blood pressure. He continued his research and practice as a member of the Mayo Clinic Staff for two years and he then returned to Duluth to resume practice of the eye, ear, nose, and throat. An amusing incident occurred at the Mayo Clinic about 1929. Doctor Anderson Hilding was born into the Anderson family and christened Hilding Anderson. He went to the Mayo Clinic under that name. While there he received notice that his services were no longer necessary and he went to the Chief of his service to tell him how sorry he was that this had to be. His Chief was amazed because he hadn't heard anything about it. It turned out that there were two Hilding Andersons at the Mayo Clinic and the termination was intended for the other one. Doctor Hilding Anderson decided that there was no use to continue such confusion and he promptly arranged for a legal change in his name from Hilding Anderson to Anderson Hilding.

Doctor Hilding published over 130 scientific papers, but is probably best known for his pioneering work on the ciliary mucus blanket of the respiratory tree. His studies were ingenious and simple, using the airway of the anesthetized calf with India ink as a marker to show the ciliary movement. When Doctor Hilding was nearly 75 years of age, he and his son David extended his observations on the cilia through the use of the electron microscope.

As the years advanced, Doctor Hilding seemed not to age, but to increase in energy and productivity. Between the ages of 70 and 85 years, he published over 30 articles in medical journals and textbooks on his current research activities, most of them relating to his continuing study of the respiratory tract. Most of his research was conducted outside of university walls in laboratory facilities furnished through St. Luke's Hospital in Duluth.

A summary of the honors bestowed upon Doctor Hilding would take many pages to list; only a few will be mentioned. He was a Clinical Professor of Otolaryngology at the University of Minnesota from 1944 with emeritus status after 1960. The Regents of the University presented him with a certificate of merit for his contributions to development of the University. In 1948 he was awarded membership in the Collegium Otorhinolaryngologicum Amicitiae Sacrum; in 1963 he received the Shambaugh Prize from the Collegium for his "excellent work on the otic capsule" and in other fields.

Doctor Anderson Hilding and Miss Inez Melander were married in 1929. Mrs. Hilding, a distinguished musician, was concert mistress for the Duluth Symphony Orchestra for many years. They had five children, the oldest of whom is David, now Professor of Otolaryngology at the University of Illinois. The Hildings are a close-knit family whose love of the out-of-doors was reflected in camping, boating, canoeing and outdoor family activity in general. One of my earliest memories of the Hildings is seeing four or five of them early on a sunny morning, rowing in a racing type boat on a small northern Minnesota lake. When Doctor Hilding was between 80 and 85 years of age he and Mrs. Hilding had a new home constructed; Doctor Hilding built the entire stone fireplace with his own hands.

Doctor Hilding's longtime secretary said that for the last two weeks of his life he seemed to be hurrying to get things finished up "in case someone beside me must carry this work on." He left the laboratory on December 2 in the afternoon to go home and begin to design a footboard which he thought would be useful for stroke patients to use to communicate when speech was not possible. He suffered a massive cerebral hemorrhage within the next 24 hours and died on December 5, 1977.

ROBERT E. PRIEST, MD

Ann Otol 87:1978

SUMMARY REPORTS ON NATIONAL-INTERNATIONAL CONFERENCES

USE OF ACOUSTIC IMPEDANCE MEASUREMENT IN SCREENING FOR MIDDLE EAR DISEASE IN CHILDREN

PLANNING COMMITTEE*

FRED H. BESS, PhD
DON A. HARRINGTON, PhD
CHARLES D. BLUESTONE, MD
JEROME O. KLEIN, MD
EARL R. HARFORD, PhD, Chairman

This report is based on formal presentations and discussions at a Symposium on Impedance Screening for Children held at Vanderbilt University School of Medicine, Nashville, Tennessee, June 20-22, 1977. The Symposium began with invited "state-of-knowledge" reports on the following aspects of middle ear disease and impedance testing in children: *Epidemiology and Natural History of Middle Ear Disease; Morbidity of Middle Ear Disease;* and *Methods of Identification of Middle Ear Disease.*

The remainder of the Symposium addressed the issue of using impedance for screening four categories of children. Each category was introduced by a state-of-knowledge report on impedance screening of: *Infants; Preschool Children; School Age Children;* and *Special Populations of Children.*

In addition, 20 papers were presented from among those submitted by investigators concerning recent studies of impedance screening in children. The Symposium had an open registration with more than 300 health professionals of varying disciplines in attendance. The format of the Symposium allowed for open discussion of both invited and selected papers. At the conclusion of the formal presentations a Task Force of 28 experts from the fields of audiology, otolaryngology, pediatrics and epidemiology met to formulate recommendations for the use of impedance screening for the detection of middle ear disease in children. In order to obtain the reactions of all persons attending the Symposium, the recommendations of the Task Force were presented and discussed at an open meeting. Although not all members of the Task Force agree with every point, the following is the consensus of the Task Force.

RECOMMENDATIONS FROM THE TASK FORCE

INTRODUCTION

Otitis media with effusion is prevalent among infants and young children. The disease is often associated with conductive hearing impairment, but the degree of this impairment varies. Moreover, the course of this type of middle ear disease is also highly variable and

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Supported in part by Grant Number MCT-000217-23-1, Maternal and Child Health Services, Bureau of Community Health Services, Public Health Service.

Complete proceedings of the "Symposium on Impedance Screening for Children" is scheduled for publication in the spring of 1978, by Grune & Stratton, Inc., New York.

*Additional Task Force Members, all of whom participated actively in the recommendations, were Samuel R. Bashore, MA, Denzil N. Brooks, MSc, Alan S. Feldman, PhD, Peggy C. Ferry, MD, Norma T. Hopkinson, PhD, Virgil M. Howie, MD, Robert W. Keith, PhD, Gunnar Lidén, MD, Robert H. Margolis, PhD, Geary McCandless, PhD, Jerry L. Northern, PhD, Jack L. Paradise, MD, Timothy J. Reichert, MD, Ulf Renvall, MD, Kenneth D. Rogers, MD, Joanne S. Rosenberg, MA, Philip E. Rosenberg, PhD, Robert J. Ruben, MD, Jay W. Sanders, PhD, Daniel M. Schwartz, PhD, Sarah H. Sell, MD, Paul A. Shurin, MD, Laura A. Wilber, PhD.

generally unpredictable. Some cases resolve spontaneously within short periods of time while others continue for months or longer. In part for these reasons, controversy exists concerning the advisability of treating this type of middle ear disease if, as is often the case, it is unaccompanied by symptoms. There is some evidence that early treatment may be of advantage in preventing certain unfavorable long-term developmental consequences in some children, but the evidence for this is not conclusive and more studies are necessary to confirm this possibility.

Of particular concern are those infants and children in whom middle ear effusion is accompanied by hearing impairment that goes unnoticed for long periods. As the number of such infants and children is thought to be large, it appears desirable to develop screening methods for identifying them. In recent years measurement of the acoustic impedance of the ear, a technique for identifying middle ear effusion and certain related disorders, has attracted widespread interest among health professionals, educators, and legislators because of its potential as a screening method.

This report is based on available information and gaps in knowledge regarding the use of impedance measurements for screening children. It suggests interim conclusions and recommendations concerning the use of impedance for screening and implies areas for future research. Since new information on this subject is being acquired rapidly, the recommendations in this report probably will require early revision.

IMPEDANCE SCREENING FOR CHILDREN

Screening is a process by which individuals are identified who may have diseases or disorders that are otherwise undetected. Middle ear disease is a disease that may prove suitable for screening because 1) it is an important health problem; 2) it has high prevalence; 3) there are accepted criteria for its diagnosis; and 4) facilities are available in many communities for its confirmatory diagnosis and its management (although in other communities such services are deficient). A fifth important criterion for suitability of the disease for screening has not been established: namely, that there is value in treating apparently nonsymptomatic children or children with little or no hearing impairment.

Impedance screening comprises either tympanometry or measurement of the acoustic reflex or both, carried out by means of electroacoustic impedance instruments, and is intended to detect the presence of middle ear effusion or of certain other less common otologic disorders. These diseases have a high degree of association with conductive hearing loss, the most common type of hearing impairment in children.

The extent varies to which impedance screening fulfills the principal criteria for an effective screening test - acceptability, reliability, validity, and reasonable cost. Impedance testing is *acceptable* to both the child and the provider of health care because it is safe, noninvasive, and simply executed. Studies have shown impedance measurement to be *reliable,* but these studies have not involved subjects of all age groups or instruments of all types in current use. The *validity* of referral criteria based on impedance measurements (i.e., their association, singly or in combination, with the presence or absence of middle ear disease) has not been established completely, and further studies are needed. In these studies, test results should be correlated with either a) otologic findings by observers whose otoscopic diagnoses have themselves been validated, or b) myringotomy findings. Minimum performance standards and design objectives of electroacoustic impedance devices are being studied by the American National Standards Institute, S-3 60. The *costs* of impedance screening are reasonable if overreferral rates are not excessive.

RECOMMENDATIONS

Because of the importance of middle ear disease in infants and children and in view of the need for additional information concerning its natural history and optimal management, the Task Force recommends that such information be sought as rapidly as possible through appropriate studies. At the present time, and until additional information has been developed, the Task Force does *not* recommend the use of impedance measurements for universal (mass) screening on a routine basis for the detection of middle ear disorders in children of any age group. Although not now recommending mass screening, the Task Force recognizes that in some locales screening programs have already been, or will be, established. Because these programs may afford opportunities to gain additional knowledge about the utility of impedance screening, the Task Force recommends that wherever possible they be designed, or their designs be modified, to accomplish this purpose. Further, the Task Force strongly recommends additional research specifically designed to evaluate impedance testing as a screening method for infants and children.

Infants (0-24 months). Middle ear effusion has its highest incidence and prevalence in the age group 6 to 24 months. Following episodes of acute infection, asymptomatic middle ear effusions continue for extended periods in a large number of infants, and there is concern about the possible effects of undetected effusions on their function and development.

Below the age of seven months the relations between tympanometric findings (using instrumentation thus far studied in this age group) and middle ear disorders are not well understood, although the limited data now available indicate that the sensitivity of tympanometry as usually performed is relatively low. Preliminary data, employing a probe tone of 660 Hz, suggest that in such infants acoustic reflex measurements may be of value in detecting middle ear effusion, and if so, might constitute an effective screening method. Additional studies on this population are required.

There are also feasibility problems associated with impedance screening of infants. Logistically it may be difficult to gather infants for testing after they leave their place of birth. Moreover, impedance testing in infants may sometimes be difficult and time consuming. Research is needed to develop for infants, screening methods which have high degrees of sensitivity, specificity, and feasibility.

Preschool and School Age Children. Even though mass screening of preschool and school age children by impedance measurements is not recommended at present, such screening is already being performed, planned or contemplated in many communities. In situations where screening is or becomes a reality, the following procedures and criteria have been judged to be minimal:

1. A combination of tympanometry and acoustic reflex measurement should be used.

2. For eliciting the acoustic reflex, a signal of 105 dB HTL should be used in the contralateral mode, or a signal of 105 dB SPL in the ipsilateral mode, or both.

3. Whether broad-band noise or pure tone is preferable as an eliciting stimulus for the acoustic reflex remains to be established. A pure tone between 1000 Hz and 3000 Hz would be acceptable for this purpose. The stimulus should be specified or described, or both.

4. Acoustic reflex measurements can be obtained either with the ear canal air pressure that results in minimum acoustic impedance or with ear canal air pressure equal to ambient pressure. The condition used should be specified.

5. For tympanometry, a 220 Hz probe tone is preferred. However, other low frequency probe tones, up to 300 Hz, are acceptable.

6. For tympanometry, an air pressure range of −400 to +100 mm H_2O is preferred. However, a range of −300 to +100 mm H_2O is acceptable. Automatic recording should be used whenever possible and the rate of air pressure change should be specified.

TABLE 1. SCHEMA RECOMMENDED FOR VARIOUS SCREENING FINDINGS

Classification	*Initial Screen*	*Retest*	*Subject Outcome*
I	Acoustic reflex present and tympanogram normal	Not required	Cleared
II	Acoustic reflex absent and/or tympanogram abnormal	Acoustic reflex absent and/or tympanogram abnormal	Referred
III	Acoustic reflex absent and/or tympanogram abnormal	Acoustic reflex present and tympanogram normal	At risk. Recheck at later date

7. Failure on the initial screening test is denoted by either an absent acoustic reflex or an abnormal tympanogram. An abnormal tympanogram is defined as one that either, a) is flat or rounded (i.e., without a definite peak), or b) has a peak at, or more negative than, −200 mm H_2O. Flat or rounded tympanograms appear to be more highly correlated with middle ear effusions than do tympanograms with peaks at negative pressure readings.

8. Any child failing the initial screening should be retested in four to six weeks. Parents or guardians should be advised accordingly. Any child who has an acoustic reflex and a normal tympanogram on the initial screening passes and is "cleared."

9. Table 1 shows the schema recommended for various screening findings. Classifications I and II should constitute the majority of children in a given population. Referral, when indicated after confirmatory retest, should be made to an appropriate health care provider in the community. Classification III constitutes a group of children that requires special monitoring by the agency responsible for the screening program. These "at risk" children should be retested periodically to determine the possible need for future medical referral. The Task Force emphasizes that more data are needed in order to further refine these screening criteria. Information concerning otologic findings and disposition in referred children is required in order to evaluate the utility of the screening process.

10. An optimal time and frequency for screening or referring particular populations cannot be advised at present because of lack of adequate information.

11. Headbands, if used, should be designed and manufactured to fit infants and small children. Probe tips should be soft and remain soft after use and cleaning. The entire probe assembly, including the tubing, should be durable.

12. Calibration of instruments should be performed routinely. This calibration should involve the intensity and frequency of the probe tone, the manometer for pressure variation, and the reflex-activating stimulus.

13. The agency responsible for a testing program must have facilities available for referral that include expert management. Prior to the initiation of a screening program, referral and management procedures must be defined.

14. Impedance testing should be supervised by professionals who are qualified by training and experience to perform and interpret impedance measurements. Because acoustic impedance testing may be performed by a variety of health specialists or paraprofessionals, there is a need for such individuals to receive specific training in the application of impedance measurements. A course, similar to that used for training industrial audiometric technicians, would offer some control of the competency of persons administering impedance screening tests. Need exists for a program similar to that of the Council for Accreditation in Occupational Hearing Conservation (COAHC). Since a nationally accepted program for training in impedance testing does not now exist, the Task Force recommends that such a course be designed by a group of pro-

fessionals with recognized qualifications. This group should specify course content, format and length, qualifications of instructors, and other related matters.

15. The cost of any screening program should be documented and should include the cost of confirmatory diagnostic tests.

16. Programs should be designed to gather information of value in defining the role of impedance measurement in screening children for middle ear disease.

Special Populations. Because of high risk, serious consequences, or known high prevalence, certain populations of children warrant special consideration for early detection of, and surveillance for, middle ear disease, beginning soon after birth. These populations are:

Children with known sensorineural hearing loss*

Developmentally delayed and mentally impaired children*

Children with cleft palate or other craniofacial anomalies

Native American children (Indian and Eskimo)

Children with Down syndrome*

CONCLUSIONS

The Task Force strongly encourages continued investigation of this method for detecting middle ear disease in infants and children. The Task Force does not endorse universal (mass) impedance screening at this time. Finally, the Task Force emphasizes the need for research to further clarify the epidemiology, natural history and optimal clinical management of middle ear disease.

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*Interpretation of acoustic reflex measurements should be made with caution in this group.

REPRINTS — Earl R. Harford, PhD, Box 396, Mayo, University Hospital, Minneapolis, MN 55455.

TERATOLOGY SOCIETY

The Teratology Society will hold its Eighteenth Annual Meeting, June 8-11, 1978 at the Grand Hotel, Mackinac Island, Michigan. For further information, contact: Eugene V. Perrin, MD, Director, Anatomic Pathology, Children's Hospital of Michigan, 3901 Beaubien Boulevard, Detroit, MI 48201.

COMMUNICATIONS

THERAPEUTIC CERVICAL TRACHEOSCOPY

David Roberts, MD
Clarence T. Sasaki, MD
New Haven, Connecticut

Recent trends indicate that the flexible fiberoptic bronchoscope has, with a few exceptions, virtually replaced the rigid scope for use in the lower tracheobronchial tree. Correspondingly, a greater proportion of rigid endoscope currently involves diagnosis and treatment of lesions in the larynx and the upper trachea. Unfortunately, less than adequate instrumentation is currently available for precise endoscopic manipulation distal to the larynx but proximal to the carina. The presently available rigid bronchoscopes are too long to allow optimum visualization and manipulation with fine instruments. On the other hand, laryngoscopes are of insufficient length to expose the cervical trachea and do not allow for easy ventilatory support. There is, in fact, no rigid scope currently available for specific use in the cervical trachea.

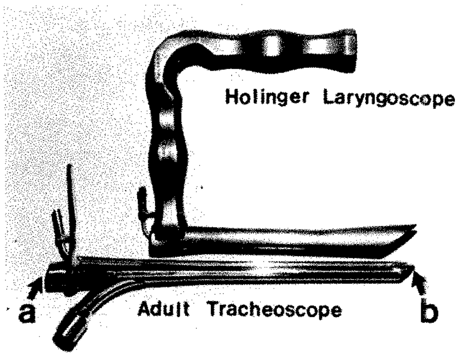

Fig. 1. Holinger laryngoscope and adult tracheoscope with bayonet fiberoptic light carrier.

The average distance from the maxillary incisors to the cricoid region in children 1-5 years of age measures 6.0 to 9.5 cm. In adults, this distance measures 14 to 15 cm. The distance to the cervical trachea adds 3 to 5 cm to these measurements in either case. Therefore, in order to achieve optimum visualization and working space in this area, separate tracheoscopes for pediatric and adult use were designed as modifications of the basic Holinger bronchoscope. The sizes selected in each case were 4 mm X 18 cm and 8 mm X 22 cm respectively. The adult scope with bayonet fiberoptic light carrier (Fig. 1) measures 22 cm from a to b. The ventilating side arm is furnished with a tip that will accept the anesthesia apparatus. Note the absence of ventilating side portals.

By virtue of their reduced overall length, these scopes allow a 30% increase in their fields of view when compared to bronchoscopes of similar internal diameter (4 mm X 30 cm, 8 mm X 40 cm). Additionally, standard center action laryngeal forceps and microlaryngeal instruments prove more than adequate in length and maneuverability and are felt to be compatible with the new design.

Our initial experience with the combination of these instruments has been rewarding in removal of tracheal foreign bodies, granulomata, and scar tissue, tasks which would be unnecessarily difficult through a flexible endoscope or rigid bronchoscope of standard length. We feel that the shorter rigid scopes, designed specifically for the cervical trachea, immensely facilitate endoscopic surgery in this area and therefore represent valid additions to existing instrumentation.

From the Department of Surgery/Section of Otolaryngology, Yale University School of Medicine, New Haven, Connecticut. This project was supported by USPHS Grant 5 RO 1 HD 09494-02.

Reprints — David Roberts, MD, Dept. of Surgery, Sec. of Otolaryngology, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06510.

BOOK REVIEWS

Hearing Loss in Children: A Comprehensive Text

Edited by *Burton Jaffe*. Hard cover, indexed, illustrated, 784 pp, 1971. University Park Press, Baltimore, MD. Price $29.50

This new text is an attempt to bring together the contributions of 55 different professionals who are concerned with hearing loss in children in a multidisciplinary approach to the problem. Physician specialists in otolaryngology, pediatrics, opthalmology, radiology, and neurology are combined with experts in the field of human communication disorders (audiology, speech, and language), psychology, education of the deaf, and social work. The book attempts to span the "state-of-knowledge" of hearing loss in children and includes the anatomy, etiology, pathogenesis, identification, diagnostic evaluation, classification, medical and surgical management, and possible effects on development and habilitation.

The concept of the text is worthwhile and long overdue. During the past ten years there has been a phenomenal information and technical explosion in almost all of the aspects covered by the book. However, the attempt to condense 57 different chapters into a relatively small book of 784 pages, has resulted in a short, superficial view of each of the areas addressed by the individual authors. Instead of a "comprehensive text" that deals in depth with many of the critical aspects of hearing loss in children, the product is an overview of the condition from the multiple authorities. It does not provide basic concepts of this broad problem, nor is a rational plan developed from early detection to habilitation. The text lacks cohesion. Fortunately, most of the chapters have excellent references which will enable the reader interested in specific problems an opportunity for further study.

The most interesting aspect of the book is the short but provocative chapters dealing with "The Effect Of Hearing Loss On Development Of Children." Especially noteworthy is the apparently original data presented by Harriet Needleman, MEd on the effects of otitis media early in childhood on speech and language development. These data appear to corroborate the original studies of Holm and Kunze that fluctuating hearing loss associated with otitis media may be associated with deficiency in the comprehension and production of the phonologic system.

In summary, this text is worth the investment for those professionals-in-training interested in hearing loss in children but exemplifies the broad scope of the problem in that it lacks the in-depth discussion of the specific subjects professionals who work with hearing handicapped children require.

CHARLES D. BLUESTONE, MD

Outcome of Severe Damage to the Central Nervous System (Ciba Foundation Symposium No. 34)

Hard cover, referenced, indexed by subject and participants, black and white illustrations, 354 pp, 1975. American Elsevier Publishing Co., Inc., New York, NY.

This volume results from a symposium that was held at the Ciba Foundation, London, in November 1974 and was chaired by Dr. F. Plum, a neurologist. The conference brought together an outstanding group of physicians and investigators from Europe and North America to examine data pertaining to the outcome of different forms of coma. It was hoped that these deliberations would serve to outline clinical and laboratory principles that would be helpful in the evaluation and treatment of patients with severe injuries to the brain and act as a scientific basis for predicting the outcome of serious neurologic disease, thus enabling the doctor to allot major efforts and realistically plan the duration and form of convalescence.

The volume is organized into individual topics in the areas of basic science and clinical studies; each topic is followed by a group discussion. There is an adequate index. The basic scientists provide an informative study of possible mechanisms of recovery in damaged central nervous systems of lower animals. However, the capacity of the human central nervous system, to either regenerate functionally after severe neurologic damage, or to repair its damage is not encouraging. The material on the effect of rehabilitative treatment on outcomes generally confirms the impression that these outcomes are strongly determined by the extent of initial injury. This is particularly so when the injury is due to stroke and, perhaps, trauma. Some of the investigations seem to indicate that early treatment and early motor retraining can favorably influence the results. Such clinical techniques as the motor response to stimulation and the oculovestibular reflex can predict the outcome of severe neurologic injury within a short time after the event and can be useful in influencing management decisions in certain patients. However, it is apparent that there is still a lack of exact information about much of the recovery curves of neurologic illnesses. Some of the studies suggest that recovery of complicated integrative behavior (*i.e.*, language function) may continue for a much longer time before the maximal benefits are reached, but the evidence for these conclusions is limited. Reports of application of mathematics and computer science to the complex medical problems associated with the recovery from severe neurologic injury hold promise of more effective decision making and outcome prediction in the future.

This book emphasizes that the brain has a limited capacity to replace its parts, or faultlessly repair its damage, and that there is still vast room for improvement in rehabilitative treatment. It should appeal to those concerned with advancing our knowledge and skills in the area of recovery from human nervous system injury.

J. A. TAREN, MD

Diseases of the Nose, Throat and Ear, Twelfth Edition

By *John Jacob Ballenger*. Hard cover, illustrated, indexed, 1118 pp, 1977. Lea and Febiger, Washington Square, Philadelphia, PA. Price $60.00

This volume represents the most recent edition of a familiar and respected companion to three generations of medical students, residents and practitioners. The author has attempted to keep pace with the continuing expansion of knowledge in otolaryngology. This has resulted in a rather concise approach to most of the specific topics covered. True to its name and previous format, the major thrust of this text is diagnosis. Anatomy and physiology are adequately covered to aid in the understanding of the pathophysiology. Medical management and surgical treatment are included but certainly not emphasized.

Important additions to this edition include new chapters on the radiology of paranasal sinuses and tomography of the temporal bone. Separate chapters reviewing the use of cryotherapy and tumor immunology have been added. A particularly nice review of the many aspects of tumor chemotherapy is also presented. The sections on endoscopy, vestibular testing and the surgical correction of facial deformities have been rewritten or expanded. Those on auditory and vestibular physiology have been updated. As in the past edition, the section on laryngology is excellent.

If this text has a failing, it is its tendency to dwell in the past rather than point to the future of the practice of otolaryngology. Sections on turbinate resection, frontal and sphenoid sinus cannulation, and Proetz therapy might be better replaced with an updated materia medica. The surgical management of vocal cord paralysis, facial nerve lesions and especially the surgical management of vertigo need to be updated. This is especially true in the face of the needlessly lengthy treatment of tonsillectomy.

Diseases of the Nose, Throat and Ear continues to be a comprehensive review of basic otolaryngologic practice aimed at a resident level. It contains about as much factual information as it is possible to squeeze into a single text. If not as flashy as some otolaryngology texts of more recent origin, it has the time-tested stability of good breeding and solid content.

RICHARD W. BABIN, MD

Diagnostics Differentiels en Oto-Rhino-Laryngologie et en Audio-Phonologie

By *J. Van Den Eeckhaut and F. Estienne.* Hard cover, indexed, 475 pp, 1976. Offixe International de Librairie S.A., Brussels, Belgium.

It is rare and pleasant to read a book which covers strictly differential diagnoses in otolaryngology and audiophonology.

Van Den Eeckhaut, in the first part, gives an extensive classification of signs and symptoms in relation to well-known syndromes in otolaryngology (hypoacusis, nasal obstruction, rhinorrhea, dysphagia). Interestingly enough, the author has tabled all these so as to make the reader think of all possibilities in the differential diagnoses. As a matter of fact, listing is so analytic that, at times, it becomes hard to follow because of numerous referrals.

In the second part, the author deals exclusively with audiophonology. Estienne, like Van Den Eeckhaut, has also divided his work into syndromes (articulatory problems, functional dysphonias, stuttering, language disorders). Definitions, characteristics, and means to get to a precise diagnosis are clear and arouse interest by the way they are offered. Here again, it is all presented in tables and schedules.

In summary, this book is not only remarkable by its original presentation but can be a useful tool in the hands of both educators and students for analytic studies of syndromes in the field of Otolaryngology and Audiophonology.

NORMAND B. GAGNON, MD

Diseases of the Temporomandibular Apparatus: A Multidisciplinary Approach

By *Douglas H. Morgan, William P. Hall, and James Vamvas.* Hard cover, indexed, black and white illustrations, 481 pp, 1977. C. V. Mosby Co., 3301 Washington Blvd., St. Louis, Mo. Price $42.50

Treating temporomandibular joint problems brings together the dental and medical professions and not only benefits the patient but the practitioners as well, enabling them to use their own special talents to help a large number of people who are affected with this problem. The book is divided into four parts: Part I pertains to growth and development and thoroughly discusses embryology and evolution, anatomy and neuroanatomy of the skeletal muscles. This part is particularly well written, especially the anatomy portion.

Part II involves all facets of diagnosis, including history taking, occlusion, radiographic procedures and their interpretation; the ear, nose and throat diagnosis.

Part III deals with a very thorough discussion of treatment, including splint, acupuncture, drugs, surgery and physical therapy.

Part IV involves developing areas, such as orthodontics, orthognathic surgery and speech problems.

This book is very well written and gives the clinician a valuable guide in treating the many problems of temporomandibular articulation.

The book is recommended for the many areas of medicine and dentistry involved in the treatment of the dysfunction of the temporomandibular joint, especially otolaryngologists and the dental specialists involved in this area of treatment.

WILLIAM H. OLIN, DDS, MS

Essays on Communication and Communication Disorders

By *William G. Hardy* and *Miriam Hardy.* Hard cover, glossary, referenced, indexed, 161 pp, 1977. Grune and Stratton, New York.

This book presents a collection of essays and lectures on communication by authors who have made a significant contribution to the speech-language and hearing literature in the medical context over the years. The authors state that some of the essays are new, having been written expressly for this book. Other essays are older and have been rewritten for the collection. The format may account for some of the redundancy in the text. Although each chapter (essay) stands alone as a cohesive logical unit, the effect of the total text is less well-organized and, at times, repetitious.

An appealing aspect of the book made possible by its format is the presentation of a broad array of concepts and ideas. This fosters another criticism, however, as the authors repeatedly tantalize the reader with a topic and then change focus before exploring issues to any depth.

The authors have included a glossary to define words and terms that recur frequently in the literature. Although some of the definitions may be improvements over those in more common sources, such as medical dictionaries, the number of omissions will likely discourage readers from using it as a frequent resource.

The authors' claim to being generalists in the field of speech pathology and audiology is supported by their consistent integration of systems involved in the communication process. It is this attitude, this concern for the total individual in the communication process, that pervades the book and makes it recommended reading.

LINDA JORDAN, PhD

ABSTRACTS FROM NATIONAL AND INTERNATIONAL JOURNALS

Squamous Carcinoma of the Lip in Queensland: A Relatively Benign Lesion

Harris TJ: Br J Plast Surg 29:68-69, 1976

The author presents a total of 219 patients with squamous cell carcinoma of the lips treated by him during the period 1966 to 1972. Commissure lesions are not included in this study. The relation to sun exposure, type of differentiation and recommended treatment are discussed.

The author notes that Queensland has an excessively high incidence of lip (and skin) cancers, that the incidence of metastasis is rare even in previously treated lesions, and that sun-induced lesions have a better prognosis after excision.

Two references are included.

M. Payne

Silastic® Implant Pharyngoplasty: Radiographic Planning and Evaluation

Evans DM, Ardran GM: Br J Plast Surg 30: 206-211, 1977

The authors review 15 patients with palatopharyngeal incompetence who had either Silastic® block or Silastic® sponge implants. Pre- and postoperative x-rays and speech assessment are the criteria of evaluation.

The technique for measuring the gap and the importance of position of the graft are discussed. Speech assessment is not further described.

Six figures including 12 excellent radiographs and four references are included.

M. Payne

Maxillofacial and Palatal Reconstructions With the Use of the Deltopectoral Flap

Bakamjian VY, Poole M: Br J Plast Surg 30:17-37, 1977

The authors illustrate the use of this multipurpose flap in still another method for radical antrectomy reconstruction. This procedure has the advantage over other methods of coverage (i.e. Owens' compound flap of cervical skin and sternocleidomastoid muscle) in that it doesn't compromise proper performance of radical neck dissection.

Seven cases are presented in detail with photographs. A total of 43 figures and 16 references are included.

M. Payne

The Role of Computed Tomography in the Management of Cancer of the Larynx

Mancuso AJ, Hanafee WN, Julliard GJ, et al: Radiology 124:243-244, 1977

These authors from the department of Radiology at UCLA describe work in progress. Computed tomography scanning can provide a more accurate appraisal of anatomy. Thyroid cartilage is well imaged and can be analyzed for symmetry of calcification and structure. Regions of anterior and posterior commissure, true and false cords and arytenoid cartilages are well seen. Nodal metastasis can be seen. Ease of examination, speed, and lack of morbidity make this an effective tool in the examination of even moribund patients.

Three figures and four references are presented.

M. Payne

Computed Tomography of Acoustic Neuroma

Davis KR, Parker SW, Neu PFJ, et al: Radiology 124:81-86, 1977

The authors from the Department of Radiology of Massachusetts General Hospital reviewed the preoperative CT scans and operative findings of each of 49 patients with acoustic neuroma and retrospectively evaluated and assessed the diagnostic capabilities of CT in the investigation of acoustic neuromas.

Prior to the availability of computed tomography preoperative work-up included skull radiographs, tomographs of the internal auditory meati and one or more invasive studies such as pneumoencephalography, Pantopaque® cisternography and angiography, often resulting in an inaccurate evaluation of the size of the lesion.

Methods and materials used are described. The cases are obtained over a 36-month period. The results showed a 20% incidence of false negative CE (contrast enhancement) scans in this series, and the Plain CT scans with no CE were obtained in 40 cases. Of these, 18 were positive, 13 of which showed displacement of the fourth ventricle as the only finding.

When tumors are smaller than 2 cm the CE scan will be normal often. False positive scans in this series are usually due to misinterpretation of artifacts from adjacent petrous bone.

The use of computer reconstruction for the production of thin sections perpendicular to the axis of the petrous bone and coronal sections has been helpful in demonstrative small lesions.

Future technical advances should improve the ability to detect and estimate the size of small lesions, improve the quality of assessment following subtotal resection, and the visualization of the internal auditory meati.

Twelve references, eight figures and one table are included.

M. Payne

Treatment of Corrosive Burns of the Esophagus

Campbell GS, Burnett HF, Ransom JM, et al: Arch Surg 112:495-500, 1977

The records of 40 patients, treated at the University of Arkansas, following ingestion of caustic material, were reviewed for data concerning the nature of the ingested material, results and the role of esophagoscopy and bougienage and the use of steroid and antibiotic therapy. Eighty percent of all patients were under 10 years of age and in 95% of the cases strong alkalis were identified as the ingested agent. Esophageal strictures formed in 45% of the cases (18/40). The use of corticosteroids appears to decrease the rate of stricture formation from 85% to 15%. No strictures developed in 87% of the patients treated with steroids and antibiotics, whereas 83% of those treated with neither steroids nor antibiotics developed strictures, usually within four weeks. Therefore, the use of steroids and broad spectrum antibiotics is recommended in all causes of esophageal burns as diagnosed by fiberoptic endoscopy.

Esophageal bougienage was useful in the dilating and management of soft annular strictures, while the long dense strictures appeared resistent and required right colon interposition.

C. Wiesenthal

Immunological Studies on So-called Nonhealing Granuloma of the Nose

Inuyama Y, Asaoka K, Nakajima Y, et al: Otolaryngology (Tokyo) 49:501-508, 1977

Immunological studies, particularly the tuberculin test (PPD) and complement (CH 50) studies measured using Mayer's method, were performed in ten cases of so-called nonhealing granuloma of the nose: two with Wegener's granulomatosis, three with reticulum cell sarcoma, and five with malignant granuloma.

A six-stage classification of tuberculin reaction and CH 50, as suggested by Nishioka and others, was employed for analysis. Stage I is defined as the stage when tuberculin reaction is intact and the CH 50 level is within normal limits. Stage II is defined as the stage when tuberculin reaction is intact; however the complement level is elevated over 45 CH 50. In stage III, the tuberculin reaction is decreased to less than a 10 mm diameter area of redness and the complement level is elevated over 45 CH 50. In Stage IV there is depressed tuberculin reactivity and a normal level of complement activity.

According to this six-stage classification, the groups which experienced remission of the disease were most frequently found in Stages I and II. On the other hand, cases with an active phase of the disease were frequently found in Stages III and IV.

The complement level was elevated during the active phase of the disease, and was depressed or fell within the normal range during the remission of the disease.

M. Igarashi

Temporal Bone Findings in Tuberculous Meningitis

Saito R, Sonobe N, Matsumura M, et al: Otolaryngology (Tokyo) 48:965-971, 1976

Tuberculous meningitis is one of the relatively rare but serious disorders with a high rate of mortality, especially for infants and the elderly. Two cases in this report were a 64-year-old male and a female infant one year and ten months old, who died of tuberculous meningitis. The temporal bones of these patients were studied histologically to determine the pathological changes in the inner ear. Both cases showed meningogenic tuberculous labyrinthitis bilaterally. The primary routes of transmission of the inflammatory process from the meningeal space appeared to be through the internal auditory canal mainly by way of the perivascular spaces of the modiolus. Perilymphatic involvement occurred first with more marked changes in the basal turn near the round window. Because of the marked pathological changes in the inner ear apparatus, it is suspected that these cases would have resulted in a profound sensorineural hearing loss and loss of vestibular function, and in the case of the infant, deafmutism, if the patients had survived.

M. Igarashi

Serial Studies of Immunocompetence in Head and Neck Cancer Patients Undergoing Radiation Therapy

Stefani S, Kerman R, Abbate J: Am J Roentgenol 126:880-886, 1976

Nonspecific immunologic parameters of 29 male patients (mean age 59 years) with confirmed malignancies of the head and neck who underwent radiation therapy were studied. The patients were apparently free of distant metastases at staging. Each patient received 1000 rads per week over a five to seven week course (mean dose 6164 rads from a Cobalt-60 source). Immunologic evaluation was conducted before and 30, 60, and 90 days after therapy.

Seventy-two percent of the patients reacted positively to two or more skin tests with microbial antigens before therapy. A marked decline in skin test reactivity was noted 90 and 180 days after treatment. Patients with pretherapy positive responses to microbial antigens had a significantly better survival than nonresponders. Similarly, 61 percent of the patients responded positively to DNCB sensitization prior to therapy, but a significant decline in reactivity to DNCB was noted after therapy.

Cancer patients demonstrated markedly lower absolute counts and percentages of B- and T-lymphocytes before therapy than controls. Absolute counts of B- and T-lymphocytes dropped significantly after therapy as did the percentage of T-lymphocytes. However, the percentages of B-lymphocytes were not altered by radiation therapy.

This study has defined the effects which radiation therapy has upon several immunologic parameters of head and neck cancer patients. Knowledge of these effects allows the otolaryngologist to better understand the immunologic ramifications of radiation therapy on the cancer patient.

J. Nysather

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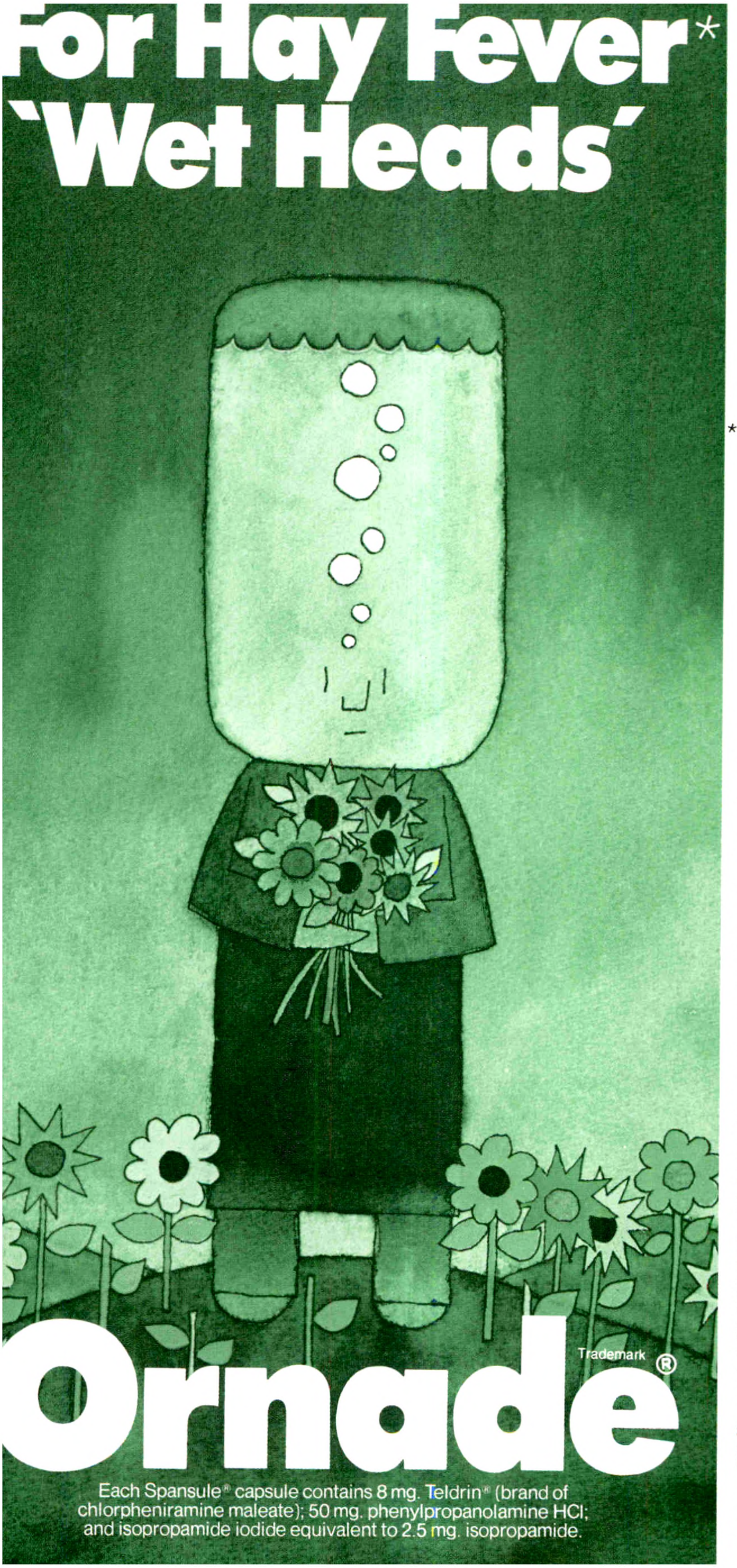

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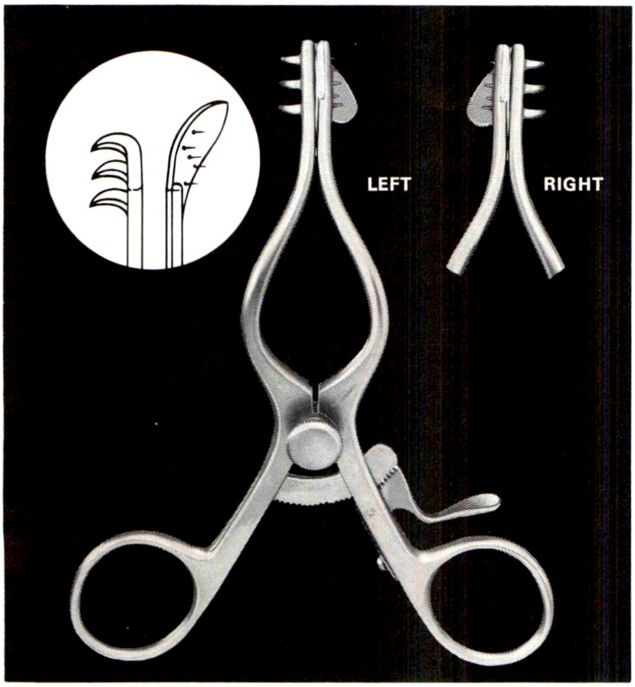

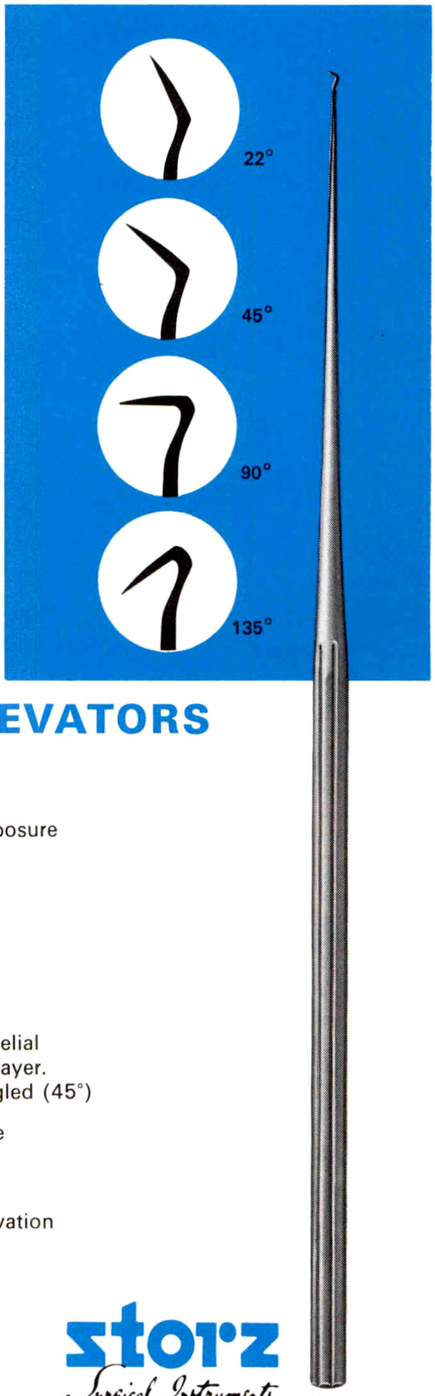

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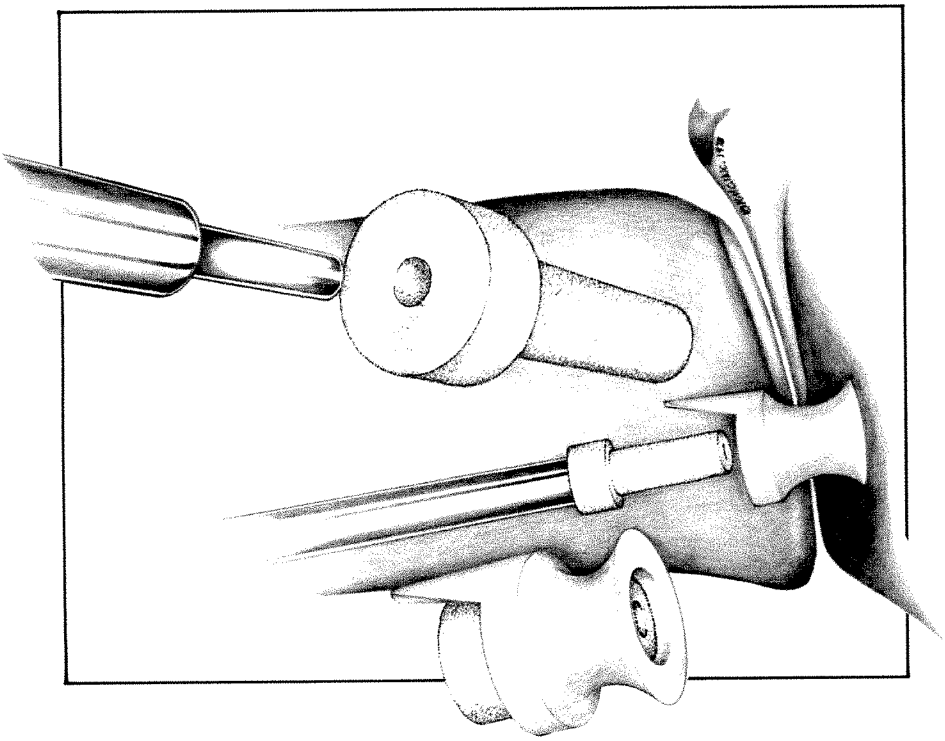

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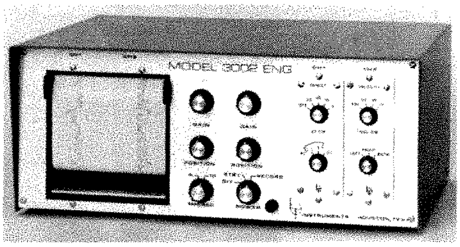

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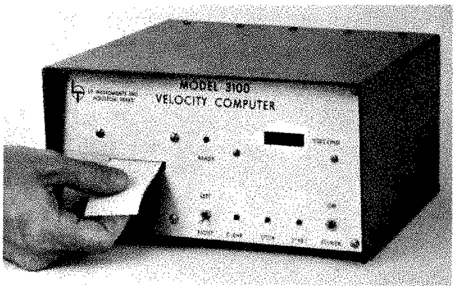

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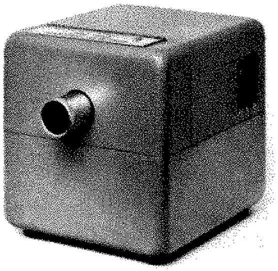

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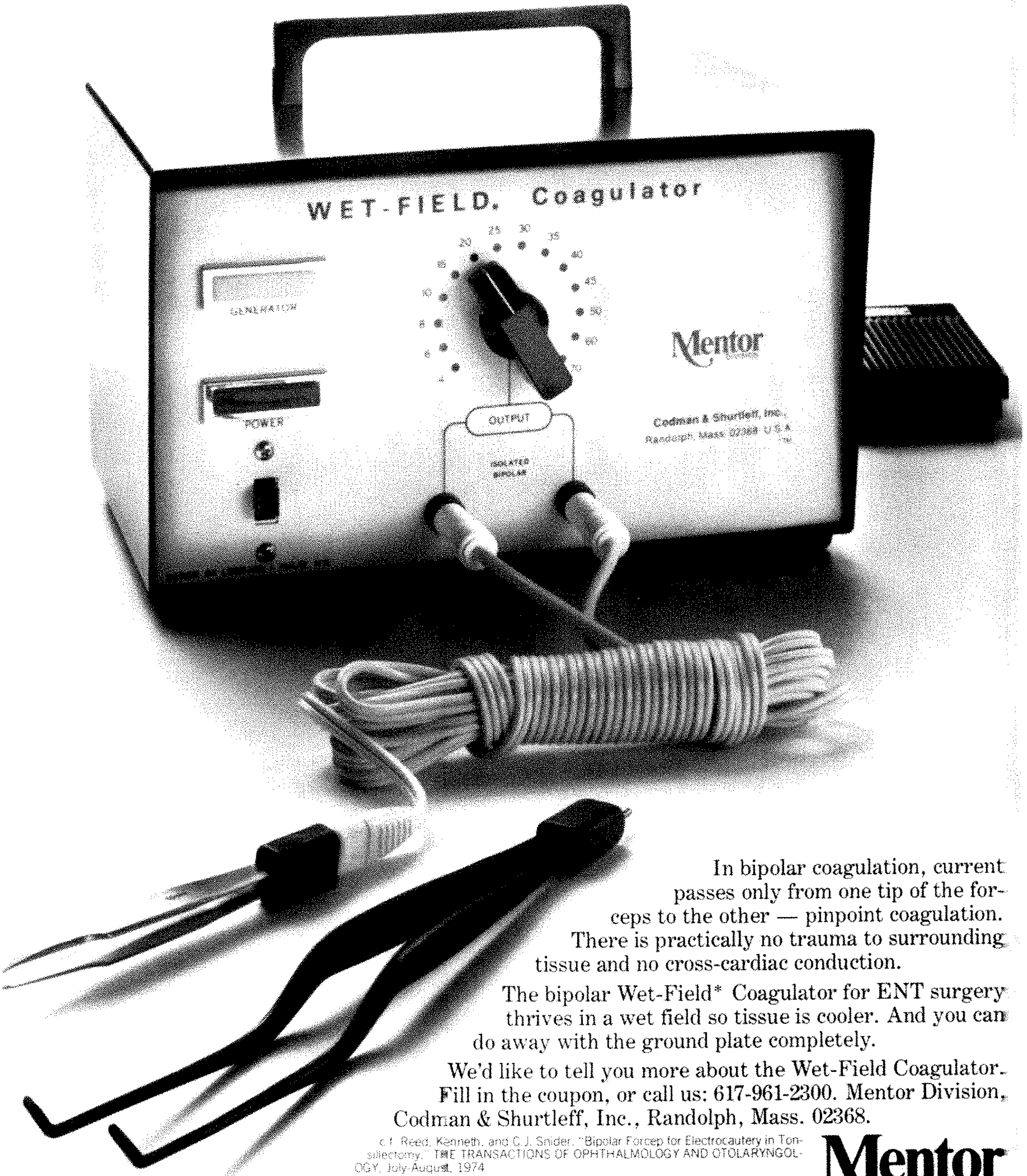

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c.f. Reed, Kenneth, and C.J. Snider, "Bipolar Forcep for Electrocautery in Tonsillectomy," THE TRANSACTIONS OF OPHTHALMOLOGY AND OTOLARYNGOLOGY, July-August, 1974

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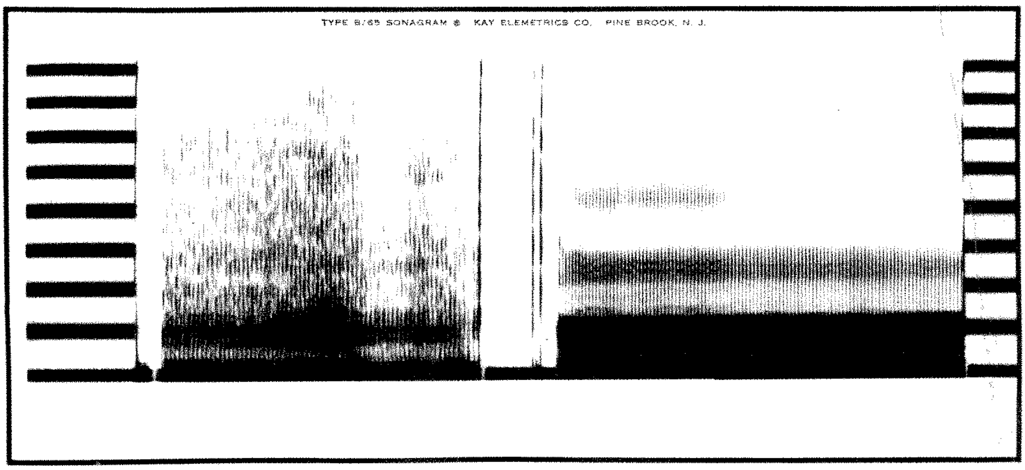

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THE ANNALS
OF OTOLOGY, RHINOLOGY & LARYNGOLOGY

ACKNOWLEDGMENTS

The Society of University Otolaryngologists gratefully acknowledges the contributive comments and criticisms of this manuscript by the Deans and Department Chairmen of the medical schools of the United States and Canada. These comments underscored the intent of this document to provide a manual for the total learning experience and not that portion confined to teaching by an Otolaryngology Department. Further, it was emphasized that complete and immediate recall of all of this information was not desirable but that it represents a description of what may be expected during the entire medical school experience.

The Society of University Otolaryngologists wishes to thank the Deans and Department Chairmen for their gracious comments and is privileged to place before them this manual.

The members of the Undergraduate Committee of the S.U.O. are indebted to Ms. Lois Bushor for her superior secretarial skills, her patience with the many manuscript revisions we imposed on her and for her constant cheerfulness throughout the long working hours in committee.

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The Society of University Otolaryngologists wishes to thank the following societies for their contribution of funds which made possible the completion of this work:

American Otological Society
American Laryngological, Rhinological and Otological Society
American Academy of Facial Plastic and Reconstructive Surgery
Society of University Otolaryngologists
Association of Academic Departments of Otolaryngology

ESSENTIAL COMPETENCIES IN OTOLARYNGOLOGY FOR THE GRADUATING MEDICAL STUDENT

SOCIETY OF UNIVERSITY OTOLARYNGOLOGISTS

Undergraduate Education Committee

Edited by

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ESSENTIAL COMPETENCIES IN OTOLARYNGOLOGY FOR THE GRADUATING MEDICAL STUDENT

SOCIETY OF UNIVERSITY OTOLARYNGOLOGISTS

Undergraduate Education Committee

INTRODUCTION

Throughout the years of medical school the student will acquire a wide variety of knowledge and skills. For administrative convenience and by tradition areas of medical science are divided into departments. Each department or academic unit will carry out its teaching responsibility according to the boundaries of its own discipline. However, the students' acquisition of the science and art of medicine only approximately recognizes these boundaries. It is a fact that the student may acquire information about a particular subject from many departments, disciplines, organ systems or individuals. This aspect is to be recommended and supported. In trying to describe the skills and knowledge in any one area of medicine the artificial boundaries of departments, disciplines, etc, must be superseded by a system that takes into account the contributions of all teaching units.

The Society of University Otolaryngologists (SUO)) undertook the task of trying to identify the competencies in Otolaryngology related fields that a medical student may be reasonably expected to encounter or acquire during the whole scope of medical school experience.

PREFACE

PURPOSE

These objectives define the minimum otolaryngologic abilities, in terms of specific behaviors that students are expected to demonstrate at the end of undergraduate medical school. The purpose of these objectives is to guide instructors, curriculum planners, students, and examiners as to what otolaryngologic competencies the Society of University Otolaryngologists (SUO) believes are essential for the graduating medical student. It is anticipated that these objectives will be achieved as a result of the total undergraduate medical school experience. These may be accomplished through a variety of learning experiences; courses, readings, rotations, etc, many of which may be under the auspices of specialties other than otolaryngology. The particular combination of learning experiences which best facilitates the students' acquisition of these competencies will be established by each medical school.

It is not the SUO's expectation that all graduating medical students will be able to, upon request, immediately demonstrate, explain or appreciate all of the competencies outlined in these objectives. However, it is the SUO's expectation that all graduating medical students will have a command of these competencies such that, in a reasonable amount of time and given appropriate resources, each student could exhibit all the outlined abilities. Individual instructors, departments, or medical schools may wish to identify portions of these abilities as "basic" or "critical" ones that their graduating medical students should have at immediate recall.

ORGANIZATION

There are many organizational outlines that objectives such as these could follow. They could be organized around headings such as anatomy, biochemistry, physiology, and pathology or they could be organized by the most frequent diseases encountered, or they could be organized by chief complaints. In selecting the most useful organization for these otolaryngologic objectives, many organizational systems were reviewed for factors such as readability, applicability to all universities, conciseness, and ease in writing.

It was felt that the most useful organizational system for these objectives, and the one used in the following pages, has the objectives initially categorized by anatomical area: ear, nose and paranasal sinuses; oral cavity and associated structures; pharynx and esophagus; larynx and trachea; and head and neck. Each of these areas has two subsections: normal and abnormal.* Within each subsection the objectives are arranged under the headings: cognitive abilities, skills, and attitudes. The cognitive objectives emphasize intellectual competencies such as knowledge, understanding and thinking abilities. The attitude objectives include those that emphasize feeling and emotion, such as interests and appreciation. The skill objectives include those that emphasize motor skills, such as removing foreign bodies or palpating an area. Finally, within the three areas (cognitive, skills, and attitudes) the objectives follow a general to specific format. The general objectives, for example, state, "The student will understand the gross anatomy of the ear." Under the general objective is a sample of specific objectives that characterize a student who "understands." For example, "The student will identify topographical anatomical features such as: the parts of the pinna (auricle), the cartilaginous and bony parts of the external auditory canal and tympanic membrane."

---

*The standard format illustrates the form of these objectives.

Since these objectives are clustered into three separate areas, cognitive abilities, skills, and attitudes, the sequence of the objectives does not follow the problem solving pattern. For example, the formulation of management plans and treatment is placed in the cognitive section, even though, in practice, the formulation of management takes place only after appropriate examination and testing, which are skills. Further, it is sometimes a question as to whether a particular competency involves more intellectual (cognitive) or manipulative (skill) abilities. For convenience "questionable objectives" have been placed arbitrarily where you see them.

The general objectives are stated in broad terms and are the goals each student should work toward. However, since these objectives are not explicit, each general objective is always followed by specific objectives which give a sample of the behaviors that characterize each general objective. The specific objectives under each general objective are not an exhaustive list of all the specific abilities one would expect a student to have if he had mastered the general objective. Instead, the sample of specific objectives outlines the domain of abilities a student would have if he had mastered the general objective.

LIMITATIONS

The objectives enumerate only the otolaryngologic competencies that are thought to be essential to the graduating medical student. Thus, many otolaryngologic competencies are purposely not included. However, it is possible that some essential competencies were inadvertently omitted or nonessential ones were inappropriately included.

Some sections are left blank because they were too obvious to enumerate. In some instances where it was felt that these points should not enter into the medical student domain they were stated as "not applicable."

Finally, the domain of otolaryngology overlaps, at times, with other specialties. Thus, some of these objectives may detail competencies which are also associated with other specialties. Conversely, it may appear that some essential otolaryngologic abilities that overlap other specialties are missing. In such cases, it was felt that these "missing" behaviors were predominately in another domain and would be more appropriately listed in another set of objectives.

STANDARD FORMAT

I. __________ (Normal)

- A. Knowledge (Cognitive)
    - *1.0* Understand the gross anatomy of __________.
      (*1.1, 1.2,* etc may be used for the gross anatomy of contiguous but separate regions.)
        - a. Identify the topographical features of such things as:
            - 1.
            - 2.
        - b. Draw and label the main anatomical features of __________.
        - c. Describe the main features of such things as:
            - 1.
            - 2.
        - d. Describe the blood supply of __________.
        - e. Describe the sensory, motor and autonomic innervation of __________.
        - f. Describe the lymphatic drainage of __________.
    - *2.0* Understand the microscopic anatomy of __________.
      (*2.1, 2.2,* etc may be used for microscopic anatomy of contiguous but separate regions.)
        - a. Describe the features of __________.
        - b. Label a diagram of __________.
    - *3.0* Understand the embryological development of __________.
      (*3.1, 3.2,* etc may be used for embryological development of contiguous but separate regions.)
        - a. Explain the differentiation of structures such as:
            - 1.
            - 2.
        - b. Describe the derivatives of structures such as:
            - 1.
            - 2.
    - *4.0* Understand the relationship of anatomical areas that are closely related to __________.
      (*4.1, 4.2,* etc may be used for relationships of anatomical areas of contiguous but separate regions.)
        - a. Describe the relationship of the __________ to such things as:
            - 1.
            - 2.
        - b. Label a schematic diagram demonstrating relationships of __________.
        - c. Explain the significance of the relationship of __________.
    - *5.0* Understand the physiology of __________.
      (*5.1, 5.2,* etc may be used for understanding the physiology of contiguous but separate regions.)
        - a. Explain the actions of the __________.
        - b. Describe the function of the __________.
        - c. Describe the production of __________.

d. Describe the characteristics of ________.

6.0 Understand the routine tests of ________.
(*6.1, 6.2,* etc may be used for understanding routine tests of contiguous but separate regions.)

a. Describe routine tests such as:

1.
2.

7.0 Understand the special tests of ________.
(*7.1, 7.2,* etc may be used for contiguous but separate regions.)

a. Describe special tests such as:

1.
2.

B. Skills

1.0 Perform an appropriate ________ examination.
(*1.1, 1.2,* etc may be used for performance of appropriate examinations of contiguous but separate regions.)

a. Identify by inspection using an appropriate source of illumination, such things as:

1.
2.

b. Identify by palpation, structures such as:

1.
2.

c. Identify by auscultation, structures such as:

1.
2.

2.0 Perform an appropriate test of ________ function.
(*2.1, 2.2,* etc may be used for performance of appropriate tests of function of contiguous but separate regions.)

a. Demonstrate sensory function.
b. Demonstrate motor function.
c. Demonstrate autonomic function.
d. Demonstrate special sensory function.

C. Attitudes

1.0 Appreciate the need for good clinical history.
2.0 Appreciate the significance of a good physical examination.
3.0 Appreciate the need for screening tests.
4.0 Appreciate the need for special tests.
5.0 Appreciate the need for preventative measures.

II. ________ (Abnormal)

A. Knowledge (Cognitive)

1.0 Understand the pathology (etiology, pathophysiology and natural history) of ________.
(*1.1, 1.2,* etc may be used for contiguous but separate regions.)

a. Describe the common lesions of ________ such as:

1. Congenital
    a)
    b)

2. Inflammatory ____________
    a)
    b)
3. Degenerative and metabolic ____________
    a)
    b)
4. Traumatic ____________
    a)
    b)
5. Neoplastic ____________
    a)
    b)
6. Psychophysiologic ____________
    a)
    b)

2.0 Formulate a differential diagnosis.

a. Prepare a differential diagnosis for chief complaints such as:
    1.
    2.

b. Defend a differential diagnosis for chief complaints such as those listed in II. A. *2.0* a.

3.0 Understand the use of routine tests for evaluation of disorders of ____________.

(*3.1*, *3.2*, etc may be used for routine tests of contiguous but separate areas or functions.)

a. Describe the principles of routine tests such as:
    1.
    2.

b. Discuss the indications of routine tests such as:
    1.
    2.

c. Interpret results of routine tests such as:
    1.
    2.

4.0 Understand the use of special tests for evaluation of disorders of ____________.

(*4.1*, *4.2*, etc may be used for special tests of contiguous but separate areas or functions.)

a. Describe the principles of special tests such as:
    1.
    2.

b. Discuss the indications of special tests such as:
    1.
    2.

c. Interpret the results of special tests such as:
    1.
    2.

5.0 Formulate a problem solving strategy for chief complaints as described in II. A. *2.0* a.

6.0 Formulate a management plan for diseases of ____________.
(*6.1*, *6.2*, etc may be used for diseases of contiguous but separate regions.)

a. Describe a treatment plan for conditions such as:
    1.
    2.

b. Explain basis for consultation and referral with an otolaryngologist for conditions such as:
    1.
    2.

B. Skills

1.0 Perform an appropriate exam of an abnormal ____________.

(*1.1*, *1.2*, etc may be used to perform an appropriate exam of an abnormal condition of contiguous but separate regions.)

a. Identify abnormalities such as:
    1.
    2.

b. Evaluate such abnormalities as described in II. B. *1.0* a.

2.0 Demonstrate the proper techniques for obtaining specimens.

a. Perform appropriate techniques for obtaining specimens.

b. Select appropriate vehicle for transporting specimens.

3.0 Exhibit appropriate treatment skills.

a. Perform appropriate medical treatment procedures for those listed in II. A. *6.0* a.

b. Perform appropriate surgical treatment procedures for those listed in II. A. *6.0* a.

C. Attitudes

1.0 Appreciate significance of early recognition of ____________.

2.0 Recognize need for habilitation and rehabilitation of ____________.

3.0 Provide community education and involvement for ____________.

LARYNX AND TRACHEA

I. Larynx and Trachea (Normal)

A. Knowledge (Cognitive)

1.0 Understand the gross anatomy of the larynx and trachea.

1.1 Understand the gross anatomy of the larynx.

a. Identify the topographical features such as:
  1. Laryngeal supraglottic area
    a) aryepiglottic fold
    b) epiglottis
    c) false vocal cord
  2. Laryngeal glottic area
    a) true vocal cords
    b) anterior commissure
  3. Laryngeal subglottic area
    a) cricothyroid membrane
    b) cricoid cartilage

b. Label a diagram of the main anatomical features of *1.1* a. 1-3.

c. Describe the blood supply such as:
  1. Superior laryngeal artery
  2. Inferior laryngeal artery
  3. Cricothyroid artery

d. Describe the sensory and motor innervations such as:
  1. Superior laryngeal nerve
    a) external branch
    b) internal branch
  2. Recurrent laryngeal nerve

e. Describe the compartmentalization of the lymphatic drainage of the larynx.

1.2 Understand the gross anatomy of the trachea.

a. Identify the topographic features.
  1. Cartilaginous rings and associated intercartilaginous membranes
  2. Common esophageal and tracheal party wall
  3. Carina
  4. T.B. tree
  5. Bronchopulmonary segments

b. Draw and label the main anatomical features of the trachea.

c. Describe the main features of such things as:
  1. Tracheal rings
  2. Party wall

d. Describe the major blood supply of the trachea.

e. Describe the major sensory and autonomic innervation of trachea and bronchi.

f. Describe briefly the lymphatic supply and drainage of the tracheobronchial tree.

2.0 Understand the microscopic anatomy of the larynx and trachea.

2.1 Understand the microscopic anatomy of the larynx.

- a. Describe the microscopic features of the epiglottis.
- b. Describe the microscopic features of the false vocal cords.
- c. Describe the microscopic features of the true vocal cords.
- d. Describe the microscopic features of the subglottis.

2.2 Understand the microscopic anatomy of the trachea.

- a. Describe the microscopic features of such things as:
  1. Tracheal mucosa
  2. Cartilages
  3. Glands
- b. Label a schematic diagram of the respiratory epithelium.

3.0 Understand the embryological development of the larynx and trachea.

3.1 Understand the embryological development of the larynx.

- a. Explain the differentiation of structures such as:
  1. Tracheal lumen

4.0 Understand the relationship of major anatomical areas and structures that are closely related to the larynx and trachea.

4.1 Understand the relationship of major anatomical areas and structures that are closely related to the larynx.

- a. Describe the relationship of the larynx to such things as:
  1. Hypopharynx and esophagus
  2. Cricopharyngeus muscle
  3. Carotid sheath and contents
  4. Thyroid and parathyroid glands
  5. Associated regional lymph nodes
- b. Label a schematic diagram illustrating the relationships of the larynx to such things as in I. A. *4.1* a.

4.2 Understand the tracheal relationship to closely related anatomical areas and structures.

- a. Describe the relationship of the trachea to structures such as:
  1. Cricoid cartilage
  2. Pretracheal fascia
  3. Right and left recurrent laryngeal nerves
  4. Esophagus
  5. Thyroid gland and its isthmus
  6. Carotid sheath
  7. Arch of aorta, innominate artery, left pulmonary artery, etc
  8. Strap muscles of the neck
  9. Suprasternal space and contents
  10. Cupula and pleura of lungs in the cervical area
  11. Inferior thyroid veins
  12. Mediastinum compartments and contents
- b. Explain significance of these relationships.
- c. Label diagrams of cross sections of neck and thorax at various levels.
- d. Describe the main features of such things as:
  1. Tracheal rings
  2. Party wall
- e. Describe the major blood supply of the trachea.
- f. Describe the major sensory and autonomic innervation.
- g. Describe briefly the lymphatic supply and drainage.

5.0 Understand the physiology of the larynx and trachea.

5.1 Understand the physiology of the larynx.
  a. Explain the action of the laryngeal structures during normal swallowing and during regurgitation such as:
    1. Sphincteric action of false cord
    2. Sphincteric action of true cord
    3. Role of epiglottis
    4. Movement of larynx and hypopharynx
  b. Describe the function of the larynx during respiration and when coughing such as:
    1. Correlation of glottic control with respiratory muscle action
  c. Describe the production of general phonatory sounds as part of speech production such as:
    1. Vibratory motion of vocal cords
    2. Pitch and loudness production
  d. Describe role of larynx in straining and lifting.
  e. Describe the vagal reflexes such as:
    1. Nasopulmonary
    2. Nasolaryngeal
    3. Laryngopulmonary
    4. Cardiopulmonary

5.2 Understand the physiology of the trachea.
  a. Explain the elongation and shortening during respiration.
  b. Describe the alteration in diameter and lumen in respiration.
  c. Describe pulmonary reflexes as listed in I. A. *5.1* e.
  d. Describe the secretory motor functions.

6.0 Understand routine tests of laryngeal and tracheal functions.

7.0 Understand special tests of laryngeal and tracheal functions.

B. Skills

1.0 Perform an appropriate laryngeal and tracheal examination.
1.1 Perform an appropriate laryngeal examination.
  a. Listen for normal sounds of breathing and phonation.
  b. Identify by palpation structures such as:
    1. Hyoid bone
    2. Thyrohyoid membrane
    3. Thyroid cartilage
    4. Cricothyroid membrane
    5. Anterior cervical chain of lymph nodes
    6. Posterior chain of lymph nodes
  c. Identify by use of head mirror or headlight structures such as:
    1. Epiglottis
    2. Vallecula
    3. Pharyngoepiglottic fold
    4. Aryepiglottic fold
    5. Arytenoid cartilage including its vocal process
    6. False cords
    7. Laryngeal ventricle
    8. True cords
    9. Shape of glottis
    10. Pyriform sinus and its neighboring structures
1.2 Perform an appropriate tracheal examination.
  a. Listen for normal tracheal airway sounds.

- b. Make visual inspection of anterior neck in tracheal area.
- c. Palpate anterior neck and identify such structures such as:
  - 1. Trachea in midline with normal motion
  - 2. Thyroid gland and isthmus
  - 3. Right and left carotid sheath area
  - 4. Borders of sternocleidomastoid muscle
  - 5. Suprasternal space area

C. Attitudes

1.0 Appreciate the need for knowing and examining laryngeal structures and functions in assessing breathing and speech.

II. Larynx and Trachea (Abnormal)

A. Knowledge (Cognitive)

1.0 Understand the pathology (etiology, pathophysiology and natural history) of the larynx and trachea.

1.1 Understand the pathology of the larynx.

- a. Describe the common lesions of the larynx such as:
  - 1. Congenital
    - a) laryngeal malacia
    - b) vocal cord paralyses (partial, complete, central, peripheral)
    - c) webs
    - d) hemangioma
    - e) clefts
  - 2. Inflammatory
    - a) infective laryngitis–viral and bacterial
    - b) croup–laryngotracheal bronchitis
    - c) supraglottis (epiglottitis)
    - d) chronic laryngitides (specific and nonspecific)
  - 3. Degenerative and metabolic
    - a) allergic laryngitis
    - b) myasthenia gravis
    - c) idiopathic vocal cord paralysis
    - d) thyroid dysfunction
    - e) senile vocal cord atrophy
    - f) rheumatoid and other collagen disorders
  - 4. Traumatic
    - a) voice abuse
    - b) postintubation
    - c) external trauma
    - d) foreign body
    - e) chemical and other various agents
  - 5. Neoplastic
    - a) papilloma
    - b) hemangioma
    - c) squamous cell carcinoma
    - d) adenocarcinoma
    - e) sarcomas
  - 6. Psychophysiologic
    - a) functional dysphonias

1.2 Understand the pathology (etiology, pathophysiology and natural history) of the trachea.

- a. Describe the common lesions of the trachea such as:
  - 1. Congenital
    - a) tracheal malacia
    - b) fistula
    - c) vascular anomalies
  - 2. Inflammatory
    - a) tracheobronchitis viral and bacterial
  - 3. Degenerative and metabolic
    - a) tracheitis sicca
  - 4. Traumatic
    - a) postintubation
    - b) postsurgical–tracheostomy
    - c) chemical, thermal, and foreign body
  - 5. Neoplastic
    - a) squamous cell carcinoma
  - 6. Psychophysiologic
    - a) chronic functional cough

2.0 Formulate a differential diagnosis.

- a. Prepare a differential diagnosis for chief complaints such as:
  - 1. Stridor, inspiratory, expiratory, and combined
  - 2. Alteration of voice; hoarseness, "hot potato" voice, aphonia, dysphonia, and odynophonia
  - 3. Cough; productive, nonproductive, nocturnal, diurnal, and paroxysmal
  - 4. Neck pain (local and referred)
  - 5. Hemoptysis
  - 6. Dyspnea (exertion or rest)
  - 7. Airway obstruction–upper and/or lower airway
- b. Defend a differential diagnosis for chief complaints such as those listed in II. A. *2.0* a. 1-7.

3.0 Understand the use of routine tests for evaluation of disorders of larynx and trachea.

4.0 Understand the use of special tests for evaluation of disorders of larynx and trachea.

4.1 Understand the use of special tests for evaluation of disorders of the larynx.

- a. Describe the principles of special tests such as:
  - 1. Pulmonary function tests
  - 2. Blood gas analysis
  - 3. Sputum cytology
  - 4. Laryngogram
  - 5. Radiological examinations
  - 6. Laryngoscopy and biopsy
- b. Discuss the indications for special tests as listed in II. A. *4.1* a. 1-5.
- c. Interpret the results of special tests such as listed in II. A. *4.1* a. 1-3.

4.2 Understand the use of special tests for evaluation of disorders of the trachea.

- a. Describe the principles of special tests such as:
  - 1. Pulmonary function tests
  - 2. Blood gas analysis
  - 3. Sputum cytology

    4. Radiological examination
        a) x-rays and tomograms
        b) contrast studies
    5. Bronchoscopy
        a) examination
        b) aspirates
        c) brushings
        d) biopsy
  b. Discuss the indications of special tests as listed in II. A. *4.2* a. 1-5.
  c. Interpret results of special tests such as those listed in II. A. *4.2* a. 1-3.

5.0 Formulate a problem solving strategy for chief complaints as described in II. A. *2.0* a. 1-5.

6.0 Formulate a management plan for diseases of larynx and trachea.
  a. Describe an initial treatment plan for conditions such as those listed in II. A. *2.0* a. 1-5.
  b. Explain the indications for supportive measures such as:
    1. Humidification
    2. Antibiotics
    3. Steroids
    4. Oxygen
    5. Respiratory support
    6. Sympathomimetics
    7. Expectorants
    8. Orotracheal intubation
    9. Tracheostomy
    10. Cricothyrotomy
  c. Explain basis for consultation and referral with an otolaryngologist for conditions such as those listed in II. A. *2.0* a. 1-5.

B. Skills

1.0 Perform an appropriate exam of an abnormal larynx and trachea.
  a. Identify and evaluate using an appropriate illumination source such abnormalities as:
    1. Subcutaneous emphysema
    2. Internal and external structural distortion
    3. Laryngeal masses
    4. Laryngeal edema
    5. Vocal cord paralysis
    6. Laryngeal infection
    7. Respiratory distress
    8. Disorder of voice
    9. Pain with speaking and/or swallowing
    10. Pain and tenderness of the thyroid alae

2.0 Demonstrate the proper techniques for obtaining specimens.
  a. Perform appropriate techniques for obtaining specimens such as:
    1. Sputum for culture
    2. Sputum for cytology
  b. Select appropriate vehicle for transporting specimens.

3.0 Exhibit appropriate treatment skills.

a. Perform appropriate medical treatment procedures for disorders such as:
   1. Acute laryngitis
   2. Croup
   3. Myasthenia gravis
   4. Allergic laryngitis
   5. Epiglottitis

b. Perform appropriate surgical treatment procedures when indicated such as:
   1. Intubation
   2. Tracheostomy
   3. Cricothyroidotomy

C. Attitudes

1.0 Appreciate significance of early recognition of hoarseness of two weeks or longer in duration.

2.0 Recognize the need for having professional support for individuals who have had a laryngectomy.

3.0 Provide community education and involvement for professional advice in voice disorders.

EAR

I. Ear (Normal)

  A. Knowledge (Cognitive)

   1.0 Understand the gross anatomy of the ear and related structures.

   1.1 Understand the gross anatomy of the external ear.

   a. Identify topographical anatomical features such as:
      1. The parts of the pinna (auricle)
      2. The cartilaginous and bony parts of the external auditory canal, and tympanic membrane

   b. Draw and label the main anatomical features of the tympanic membrane.

   c. Describe the main features of such things as:
      1. The pars flaccida
      2. The pars tensa

   d. Explain the innervation of the external ear and tympanic membrane.

   e. Describe the main blood supply to the external ear and tympanic membrane.

   1.2 Understand the gross anatomy of the middle ear and mastoid.

   a. Identify the structures of the middle ear such as:
      1. Ossicles and their muscular tendons
      2. Eustachian tube orifice
      3. Chorda tympani nerve
      4. Oval and round windows
      5. Promontory (basal coil of cochlea)
      6. Facial nerve

   b. Describe the main anatomical features of the mastoid and middle ear such as:
      1. Mastoid antrum and air cells
      2. Epitympanum, mesotympanum and hypotympanum
      3. Sigmoid sinus plate
      4. Posterior fossa plate
      5. Middle fossa plate

   c. Describe the sensory and motor innervation of the middle ear structures such as:
      1. Medial aspect of the tympanic membrane and the middle ear walls
      2. Stapedial muscle
      3. Tensor tympani muscle

   1.3 Understand the gross anatomy of the inner ear.

   a. Identify the bony and membranous inner ear structures.

   b. Identify the main anatomical features of the inner ear such as:
      1. Cochlea
      2. Vestibule
      3. Vestibular labyrinth
      4. Internal auditory canal

- c. Describe the main features of the membranous vestibular labyrinth such as:
  - 1. Spatial orientation of semicircular canals
  - 2. Utricle and saccule
- d. Identify the parts of the cochlea, such as:
  - 1. Scala vestibuli, scala media, scala tympani
  - 2. Oval and round windows
- e. Identify the endolymph and perilymph compartments.
- f. Describe the VIII nerve (acoustic nerve) and its components.
  - 1. Auditory nerve
  - 2. Vestibular nerve
- g. Describe the origin and distribution of the blood supply to the inner ear.

1.4 Understand the gross anatomy of the facial nerve.

- a. Describe the course of the facial nerve from the brainstem to terminal innervation of its branches.
- b. Identify the branches of the facial nerve including:
  - 1. Greater superficial petrosal
  - 2. Stapedial
  - 3. Chorda tympani
  - 4. The five terminal
- c. Describe the motor, sensory and autonomic components of the facial nerve.

2.0 Understand the microscopic anatomy of the ear and related structures.

2.1 Understand the microscopic anatomy of the external ear, middle ear, and mastoid such as:

- a. Describe the mucosal lining of the Eustachian tube.
- b. Describe the mucosal lining of the middle ear and mastoid.

2.2 Understand the microscopic anatomy of the inner ear.

- a. Identify the structural components of the cochlea such as:
  - 1. Scala media, scala vestibuli, scala tympani
  - 2. The organ of Corti and its cellular components
  - 3. Basilar membrane
  - 4. Stria vascularis
  - 5. Spiral ganglion
  - 6. Round window membrane
  - 7. Cochlear aqueduct
- b. Identify the structural components of the vestibule and vestibular labyrinth such as:
  - 1. Footplate in oval window
  - 2. Maculae of saccule and utricle
  - 3. Cristae of semicircular canals and the canals
  - 4. Endolymphatic duct and sac

3.0 Understand the embryological development of the ear.

- a. Identify the origin of the external and middle ear from the first and second branchial arch.
- b. Identify the inner ear as being derived from the otic placode.

4.0 Understand the anatomical relationships of the ear to surrounding structures.

4.1 Understand the anatomical relationship of the external ear to surrounding structures.
  a. Describe the relationship of external ear to the temporal mandibular joint.
  b. Describe the relationship of external ear to the parotid gland.

4.2 Understand the anatomical relationship between the middle ear and mastoid and surrounding structures.
  a. Describe the relationship of the middle ear and mastoid to such things as:
    1. Inner ear
    2. Eustachian tube and nasopharynx
    3. Facial nerve
    4. Oval and round windows
    5. Posterior and middle fossa
    6. Jugular foramen, jugular vein and the carotid artery
  b. Label a schematic diagram demonstrating relationships of the middle ear contents to surrounding structures.

4.3 Understand the relationship of the inner ear to surrounding structures.
  a. Describe relationship of the internal auditory canal to cerebellopontine angle.
  b. Describe relationship of petrous apex to cranial nerves V - XIII.

5.0 Understand the physiology of the ear.

5.1 Understand physiology of hearing.
  a. Explain the physical properties of sound.
  b. Describe the transmission of sound through the external ear and middle ear to the inner ear.
  c. Explain the impedance matching system of the middle ear, such as. the hydraulic amplification effect achieved because of the difference in size between the tympanic membrane and the stapes footplate, and the lever effect of the ossicular chain.
  d. Explain the function of the inner ear in sound perception and central transmission, such as:
    1. Describe the vibratory pattern of the basilar membrane in response to stimulation.
    2. Describe hair cell excitation.
    3. Describe the neural pathway from the hair cells to the acoustic cortex.
  e. Describe the frequency range of the ear and frequency range important for speech.
  f. Describe the psychoacoustic properties of hearing such as:
    1. Explain intensity vs loudness
    2. Explain sound localization
    3. Explain the relationship between pitch and frequency
    4. Explain speech discrimination
    5. Explain central auditory function
  g. Explain the importance of hearing as it relates to the development of speech and the development of language.

5.2 Understand the function of the vestibular system in the normal maintenance of balance.
  a. Describe the multiple systems that contribute to the subservance of normal balance maintenance, such as the vestibular system,

the proprioceptor system, the visual system, and the central nervous system.

- b. Explain the mechanism of stimulation of the semicircular canal cristae.
- c. Explain the mechanism of stimulation of the maculae of the utricle.
- d. Explain the relationship of vestibular stimulation to the oculomotor system.
- e. Explain vestibular nystagmus.
- f. Explain the normal response of a subject to angular acceleration by a rotational stimulus such as:
    1. Nystagmus
    2. Vertigo
    3. Past pointing
    4. Tendency to fall
    5. Extremity reflexes
    6. Autonomic responses

5.3 Understand facial nerve physiology.

- a. Describe the somatic motor and sensory functions.
- b. Describe the visceral motor and sensory functions.

5.4 Understand the physiology of the Eustachian tube.

- a. Explain the normal ventilation of the middle ear dependence on Eustachian tube function.
- b. Describe how normal hearing is influenced by midde ear ventilation.
- c. Relate Eustachian tube opening and closing to such things as swallowing.

6.0 Understand routine tests of the ear.

6.1 Understand routine tests of hearing in adults and children.

- a. Explain tests by tuning forks, such as:
    1. Rinne
    2. Weber
    3. Schwabach
- b. Describe whispered voice and "watch" tests.
- c. Describe pure tone screening audiograms.

6.2 Understand routine tests of vestibular function.

- a. Explain the response of a subject to caloric tests such as:
    1. Minimal ice water caloric
- b. Explain the response of a subject to oculomotor tests such as:
    1. Gaze testing
    2. Positional testing
- c. Explain the response of a subject to neurological tests such as:
    1. Romberg and tandem Romberg
    2. Past pointing

6.3 Understand tests of routine facial nerve function.

- a. Describe facial nerve excitability testing.
- b. Describe central and peripheral mechanism of facial expression.

7.0 Understand special tests of the ear.

7.1 Understand special tests of hearing.

- a. Explain pure tone and speech audiograms.
- b. Explain impedance audiometry.

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- c. Identify tests for cochlear and retrocochlear function such as:
    - 1. Tone decay
    - 2. Recruitment
    - 3. SISI
    - 4. Békésy
    - 5. Speech discrimination

7.2 Understand special tests of vestibular function.

- a. Explain the Hallpike bithermal caloric test.
- b. Explain ENG testing.
- c. Describe principles of optokinetic testing.
- d. Describe tests of facial nerve function such as:
    - 1. EMG
    - 2. Tearing
    - 3. Stapedial reflex
    - 4. Taste

7.3 Describe the principles of radiological tests such as:

- 1. Panorex
- 2. TMJ
- 3. Skull and sinus
- 4. Mastoids
- 5. Polytomes
- 6. Computerized axial tomography
- 7. Brain scan
- 8. Angiography
- 9. Pneumoencephalography
- 10. Soft tissue of neck

7.4 Describe the principles of ancillary tests such as:

- 1. CBC
- 2. UA
- 3. FTA
- 4. GTT
- 5. Thyroid profile
- 6. Lipoprotein profile
- 7. Cultures of pus

B. Skills

1.0 Perform an appropriate examination of the ear and related structures.

1.1 Perform an appropriate examination of the ear and hearing apparatus.

- a. Identify by inspection using an appropriate source of illumination such things as:
    - 1. The symmetry of the pinna and the external ear.
    - 2. Demonstrate pertinent anatomical landmarks of the tympanic membrane such as:
        - a. Pars flaccida
        - b. Pars tensa
        - c. Light reflex
        - d. Short process of malleus
        - e. Long process of malleus
        - f. Umbo
- b. Identify the mobility of the TM by pneumootoscopy.

        c. Evaluate hearing thresholds by performing screening tests such as:
            1. Using conversational and whispered voice, each ear separately.
            2. Performing tuning fork tests, Rinne, Weber, Schwabach, etc.
    1.2 Perform an appropriate vestibular examination by such things as:
        a. Inspection of eyes for nystagmus
        b. Perform a neurological evaluation of cranial nerves
        c. Perform test of balance and coordination such as:
            1. Romberg
            2. Heel-toe
            3. Past pointing

II. Ear (Abnormal)
- A. Knowledge (Cognitive)
    - *1.0* Understand the pathology (etiology, pathophysiology and natural history) of the ear.
    - *1.1* Understand the pathology (etiology, pathophysiology and natural history) of the external ear.
        - a. Describe the common lesions of the external ear such as:
            - 1. Congenital
                - a) agenesis and atresia
                - b) microtia and synotia
                - c) lop ear
            - 2. Inflammatory
                - a) external otitis: viral, bacterial, fungal, dermatologic, allergic
                - b) perichondritis
                - c) herpes zoster oticus
            - 3. Degenerative and metabolic
                - a) gout (tophi)
                - b) relapsing polychondritis
            - 4. Traumatic
                - a) hematoma
                - b) laceration
                - c) frostbite
                - d) burn
                - e) foreign body
            - 5. Neoplastic
                - a) basal cell carcinoma
                - b) squamous cell carcinoma
                - c) melanoma
                - d) exostosis and osteoma
                - e) histiocytosis X
                - f) rhabdomyosarcoma
            - 6. Psychosomatic
                - a) none
    - *1.2* Understand the common lesions of the middle ear and mastoid.
        - a. Describe the common lesions of the middle ear cleft such as:
            - 1. Congenital
                - a) ossicular malformations
                - b) agenesis

2. Inflammatory
    a) serous otitis media
    b) suppurative otitis media
    c) complications of serous and suppurative otitis media
    d) mastoiditis
    e) tympanosclerosis
    f) cholesteatoma
3. Degenerative and metabolic
    a) otosclerosis
4. Traumatic
    a) barotrauma
    b) ossicular disruption
    c) tympanic membrane perforation
    d) hemotympanum
5. Neoplastic
    a) glomus jugulare
6. Psychosomatic
    a) none

1.3 Understand the common lesions of the inner ear.

a. Describe the common lesions of the inner ear such as:
1. Congenital
    a) Hereditary, such as:
        1) Alports' syndrome
        2) Pendred's syndrome
        3) Usher's syndrome
        4) Waardenburg's syndrome
    b) Acquired, such as:
        1) rubella
        2) cytomegalic inclusion disease
        3) ototoxicity
        4) prematurity
2. Inflammatory
    a) labyrinthitis; viral, bacterial (meningogenic or otogenic), and toxic
3. Degenerative and metabolic
    a) presbycusis
    b) Ménière's disease
    c) ototoxicity
    d) diabetes mellitus
    e) sudden deafness
4. Traumatic
    a) noise induced hearing loss
    b) acoustic trauma
    c) fracture of the temporal bone
    d) concussion
5. Neoplastic
    a) none
6. Psychosomatic
    a) functional hearing loss

1.4 Understand the common lesions of the facial nerve.

a. Describe the common lesions of the facial nerve such as:
1. Congenital
    a) aplasia

2. Inflammatory
a) idiopathic facial paralysis
b) hyperkinesia (hemifacial spasm)
3. Explain facial nerve degeneration and regeneration
a) Explain Wallerian degeneration
b) Describe nerve regeneration
c) Distinguish neuropraxia from degeneration by describing appropriate testing techniques.
4. Traumatic
a) surgical
b) temporal bone fracture
c) facial laceration
5. Neoplastic
a) facial nerve neuroma
b) parotid tumor
c) acoustic neuroma
6. Psychophysiologic
a) simple tic

2.0 Formulate a differential diagnosis for chief complaints.
a. Prepare a differential diagnosis for chief complaints such as:
1. Otalgia (primary and referred)
2. Tinnitus (objective and subjective; continuous and pulsatile)
3. Hearing loss (organic and functional; unilateral)
4. Dizziness (central and peripheral)
5. Otorrhea (sanguinous, watery and purulent)
6. Facial paralysis (central and peripheral)
b. Defend a differential diagnosis for chief complaints as described in II. A. *2.0* a. 1-6.

3.0 Understand the use of routine tests for evaluation of the abnormal ear.
a. Describe tests such as those in I. A. *6.0* (*6.1*, *6.2*, *6.3*).
b. Discuss indications for routine tests as described in II. A. *3.0* a.
c. Interpret the results of routine tests as described in II. A. *3.0* a.

4.0 Understand special tests for the evaluation of ear disorders.
a. Describe the principles of such tests as those in I. A. *6.0* (*6.1*, *6.2*, *6.3*) and I. A. *7.0* (*7.1*, *7.2*, *7.3*, *7.4*).
b. Discuss indications for tests such as described in I. A. *6.0* (*6.1*, *6.2*, *6.3*).
c. Interpret results of tests such as described in I. A. *6.0* (*6.1*, *6.2*, *6.3*).

5.0 Formulate a problem-solving strategy for chief complaints listed in II. A. *2.0* a. 1-6.

6.0 Formulate appropriate management plan for diseases of the ear.
a. Explain a treatment plan for conditions such as those listed in II. A. *1.1* a. 2. a) & II. A. *1.2* a. 2. a)
2. b) 2. b)
2. c)
4. a)
4. b)
4. c)
4. d)
4. e)

b. Explain the basis for consultation and referral with an otolaryngologist for conditions such as those listed in II. A. *1.0* (*1.1, 1.2, 1.3, 1.4*).

B. Skills

1.0 Perform an appropriate examination of an abnormal ear.

a. Identify by appropriate examination such abnormalities as:

1. Microtia and synotia
2. Lop ear
3. Erythema and edema of pinna
4. Auricular and mastoid tenderness
5. Meatal obstruction by:
    - a) cerumen
    - b) foreign body
    - c) edema
    - d) exudate
    - e) stenosis
    - f) cholesteatoma
6. Neoplasm of external ear
7. Tympanic membrane abnormality
    - a) retraction
        - 1) attic
        - 2) pars tensa
    - b) bulging
    - c) infection
    - d) perforation
        - 1) central
        - 2) marginal
    - e) pulsation
    - f) vesicles
    - g) cholesteatoma
    - h) serous otitis media
    - i) restricted mobility of tympanic membrane
    - j) tympanosclerosis

b. Identify alterations in hearing by appropriate tests.

c. Identify alterations in balance, including nystagmus by appropriate tests.

d. Identify facial nerve weakness by appropriate tests.

e. Evaluate by appropriate examination such abnormalities as those described in II. B. *1.0* a-d.

2.0 Demonstrate proper techniques for obtaining appropriate specimens.

3.0 Demonstrate treatment techniques.

a. Prescribe medical treatment for such conditions as listed in II. A. *6.0* a.

b. Perform surgical treatment procedures such as:

1. Simple foreign body and cerumen removal
2. Simple pinna lacerations

C. Attitudes

1.0 Recognize the significance of early recognition of effects of hearing loss in infancy.

a. Distinguish profound hearing loss from mental retardation.

b. Predict hearing loss on speech and language development.

2.0 Recognize need for habilitation and rehabilitation of sensorineural hearing loss.

a. Explain indications and benefits of appliances such as:
   1. Hearing aid

b. Explain indications and benefits of services such as:
   1. Lip reading
   2. Special schools
   3. Speech therapy
   4. Genetic counseling
   5. Follow-up examinations

ORAL CAVITY AND ASSOCIATED STRUCTURES

I. Oral Cavity and Associated Structures (Normal)

A. Knowledge (Cognitive)

1.0 Understand the gross anatomy of the oral cavity and related structures.

- a. Identify important topographical features of the oral cavity such as:
  1. Anterior 2/3 tongue
  2. Lingual frenulum
  3. Submandibular gland and duct (Wharton's duct)
  4. Parotid gland duct (Stensen's duct)
  5. Hard palate
  6. Soft palate
  7. Anterior faucial pillar
  8. Alveolar ridges
  9. Retromolar trigone
  10. Dentition
  11. Floor of mouth
  12. Mandible and temporal mandibular joint
- b. Describe the major and minor salivary glands including their intraoral orifices.
- c. Describe the main features of deciduous and permanent dentition.
- d. Describe the lymphatic drainage of the various segments of the oral cavity and salivary glands.
- e. Describe sensory and motor innervation of the oral cavity.

2.0 Understand the microscopic anatomy of the oral cavity and related structures.

- a. Lingual papillae
- b. Major and minor salivary glands and ducts
- c. Oral mucous membrane

3.0 Understand the embryological development of the oral cavity.

- a. Describe the origin of the tongue.
- b. Describe the origin of the hard palate.
- c. Describe the origin of the soft palate.
- d. Describe the origin of dental and gingival structures.
- e. Describe the differentiation of first branchial arch and cleft.

4.0 Understand the relationships of anatomic structures and areas that are closely related to the oral cavity.

4.1 Understand the relationship of anatomical areas that are closely related to the hard and soft palate.

- a. Describe the relationship of the hard and soft palate to such things as:
  1. Maxillary sinus
  2. Floor of nose

4.2 Understand the relationship of anatomical areas that are closely related to the tongue and floor of the mouth.
  a. Describe the relationship of the tongue and floor of the mouth to such structures as:
    1. Submandibular duct and gland
    2. Hyoid bone
    3. Hypoglossal nerve
    4. Lingual nerve

4.3 Understand the relationship of anatomical areas that are closely related to the mandible.
  a. Describe the relationship of the mandible to such structures as:
    1. Maxilla
    2. Dentition and occlusion
    3. Deep neck spaces
    4. Temporal mandibular joint

5.0 Understand the physiology of the oral cavity.

5.1 Understand the physiology of the oral phase of deglutition and digestion.
  a. Explain the physiology of deglutition by describing such things as:
    1. Mastication
    2. The actions of the intrinsic and extrinsic muscles of the tongue
    3. The function of the temporal mandibular joint
    4. The composition, production and functions of saliva

5.2 Understand the physiology of the gustatory system.
  a. Explain the physiology of the gustatory system by describing such things as:
    1. The four main tastants
    2. The relationship of taste and smell
    3. The chemical stimulation of taste buds

5.3 Understand the role of the oral cavity in speech.
  a. Describe in general terms the mechanism of sound modulation and articulation by:
    1. The teeth
    2. The palate
    3. The tongue
    4. The lips

5.4 Understand the respiratory role of the oral cavity.
  a. Describe the amount of humidification achieved by the oral cavity.
  b. Decribe the airway dead space of the oral cavity.

6.0 Understand the routine tests of the oral cavity and related areas.
  a. Describe the principles of routine tests such as:
    1. Culture and sensitivity
    2. Routine dental and panorex x-rays of the jaws
    3. Motor function of tongue and palate

7.0 Understand the use of special tests for the oral cavity and related areas.
  a. Describe the principles of special tests such as:
    1. Salivary flow
    2. Salivary gland scanning
    3. Sialography
    4. Polytomography of the facial skeleton
    5. Speech evaluation

6. Biopsy
7. CBC, ESR, immunoelectrophoresis, calcium, phosphorus, uric acid, BUN, creatinine, glucose tolerance, serum proteins, FTA, monospot, LE prep, RA factor
8. Sweat test

B. Skills

1.0 Perform an appropriate examination of the oral cavity and related structures.

- a. Using a head mirror or other light source, inspect such things as:
  1. Tongue (anterior 2/3 and posterior 2/3, dorsal and ventral surfaces)
  2. Gingiva and teeth
  3. Buccal mucosa
  4. Faucial pillars
  5. Salivary duct orifices
- b. Palpate with gloved finger or bimanually such things as:
  1. Tongue, including base of tongue
  2. Gingivo-lingual sulcus structures
  3. Mandible
  4. Submandibular glands and ducts
  5. Parotid gland and duct
- c. Demonstrate the normal motor function of such things as:
  1. Tongue
  2. Soft palate
  3. Lips

C. Attitudes

1.0 Appreciate the need for good oral hygiene.

- a. Demonstrate the proper techniques for dental cleaning.
- b. Identify the patient that needs referral for dental evaluation and treatment.
- c. Explain the harmful effects of tobacco and alcohol in the short and long term.

II. Oral Cavity and Associated Structures (Abnormal)

A. Knowledge (Cognitive)

1.0 Understand the pathology (etiology, pathophysiology and natural history) of the oral cavity and related structures.

1.1 Understand the pathology (etiology, pathophysiology and natural history) of the oral cavity.

- a. Describe common lesions of the oral cavity such as:
  1. Congenital
     - a) cleft palate and cleft lip
     - b) ankyloglossia
     - c) first branchial arch abnormalities
     - d) macroglossia
     - e) Fordyce spots
  2. Inflammatory
     - a) aphthous ulcers
     - b) gingivitis
     - c) glossitis
     - d) stomatitis (viral, fungal, and bacterial)
     - e) dental caries

3. Metabolic and degenerative
    a) hypovitaminosis
    b) allergy and hypersensitive reactions
    c) autoimmune diseases
    d) granulomatous disorders
    e) "sicca" syndromes
    f) cysts of dental origin
4. Traumatic
    a) pyogenic granuloma
    b) lacerations
    c) thermal, caustic, electrical burns
5. Neoplastic
    a) leukoplakia
    b) squamous cell cancer
    c) sarcoma
    d) adenocarcinoma
    e) lymphangioma
    f) hemangioma
    g) dental tumors
6. Psychophysiologic
    a) burning tongue
    b) bruxism
    c) cacogeusia

1.2 Understand the pathology (etiology, pathophysiology and natural history) of the major salivary glands.

a. Describe common lesions of the salivary glands such as:
1. Congenital
    a) sialectasis
2. Inflammatory
    a) viral sialadenitis
    b) suppurative sialadenitis
3. Metabolic and degenerative
    a) calculi
    b) calculus sialadenopathy (benign lymphoepithelial lesion)
    c) dehydration
4. Traumatic
    a) lacerations (parotid duct, parotid gland)
    b) ranulae
5. Neoplastic
    a) benign tumors
        1) pleomorphic adenoma
        2) papillary cystadenoma lymphomatosum
        3) oncocytoma
    b) malignant tumors
        1) squamous cell carcinoma
        2) adenoidcystic carcinoma
        3) acinic cell adenocarcinoma
        4) mucoepidermoid adenocarcinoma
        5) lymphoma

2.0 Formulate a differential diagnosis.

a. Prepare a differential diagnosis for chief complaints such as:
1. Pain in oral cavity
2. Oral cavity lesion

        3. Trismus
        4. Difficulty with mastication
        5. Bleeding in the oral cavity
        6. Dry mouth
        7. Expressive salivation
        8. Bad taste and/or halitosis
        9. Swelling
        10. Fractured tooth
        11. Difficulty with articulation
        12. Tongue-tie
        13. Salivary gland swelling and/or pain
    b. Defend the differential diagnosis for chief complaints of such things as those listed in II. A. *2.0* a. 1-13.

3.0 Understand the use of routine tests of the oral cavity and salivary glands.

    a. Describe the principles of routine tests such as those listed in I. A. *6.0* a. 1-3.

    b. Discuss the indications for the routine tests listed in II. A. *3.0* a.

4.0 Understand the use of special tests for the evaluation of disorders of the oral cavity and salivary gland.

    a. Describe the principles of special tests such as those listed in I. A. *7.0* a. 1-8.

    b. Discuss the indications for special tests such as those listed in II. A. *4.0* a.

    c. Interpret the results of special tests of such things as those listed in II. A. *4.0* a. 7 and 8.

5.0 Formulate a problem solving strategy for chief complaints as those listed in II. A. *2.0* a. 1-13.

6.0 Formulate a management plan for diseases of the oral cavity and salivary glands.

    a. Describe a treatment plan for conditions such as those listed in II. A. *1.1* and *1.2*.

    b. Explain the basis for consultation and referral with an otolaryngologist for conditions such as those listed in II. A. *1.1* and *1.2*.

B. Skills

1.0 Perform an appropriate exam of an abnormal oral cavity and associated structures.

1.1 Perform an appropriate examination of an abnormal oral cavity.

    a. Identify abnormalities such as:
        1. Cleft of the lip and palate
        2. Neoplastic and inflammatory lesions of the oral cavity mucosa
        3. Infections of the oral cavity
        4. Mucosal ulcers
        5. Red orifice of Stensen's duct
        6. Stone in Wharton's duct
        7. Poor oral hygiene
        8. Mucosal stippling
        9. Specifically identify integrity of tonsillar-lingual sulcus
        10. Torus palatinus and mandibularis
        11. Bifid uvula and short palate
    b. Evaluate such abnormalities such as described in II. B. *1.1* a. 1-11.

1.2 Perform an appropriate exam of abnormal salivary glands.
- a. Identify abnormalities such as:
  1. Purulence from Stensen's duct
  2. Stone in Wharton's duct
  3. Diffuse salivary gland swelling
  4. Localized swelling within salivary gland
  5. Salivary gland tenderness
  6. Absence of salivary gland flow
  7. Xerostomia
- b. Evaluate such abnormalities as described in II. B. *1.2* a. 1-7.

2.0 Demonstrate the proper techniques for obtaining specimens.
- a. Perform appropriate techniques for obtaining specimens for culture.

3.0 Exhibit appropriate treatment skills.
- a. Perform appropriate medical treatment procedures for such things as:
  1. Aphthous ulcers
  2. Gingivitis
  3. Simple stomatitis
  4. Uncomplicated allergic and hypersensitive reactions
  5. Bruxism
  6. Simple sialadenitis
- b. Perform appropriate surgical treatment for conditions such as:
  1. Simple lacerations

C. Attitudes

1.0 Recognize the significance of early recognition of white lesions in the mouth.

2.0 Recognize the need for habilitation and rehabilitation of degenerative conditions of dentition and jaws.

3.0 Recognize the need for good oral hygiene.

HEAD AND NECK

- I. Head and Neck (Normal)
  - A. Knowledge (Cognitive)
    - *1.0* Understand the gross anatomy of the head and neck region.
    - *1.1* Understand the gross anatomy of the head.
      - a. Identify the topographical features such as:
        - 1. Soft tissue landmarks such as:
          - a) inner and outer canthus
          - b) nasolateral folds
          - c) angle of mouth
          - d) philtrum, vermilion border
          - e) mentum
        - 2. Wrinkle lines
        - 3. Bony prominences such as:
          - a) orbital rims
          - b) zygomatic and malar eminences
          - c) maxilla
          - d) nasal dorsum
          - e) premaxilla
          - f) mandible including
            - I. ramus
            - II. angle
            - III. body
            - IV. symphysis
      - b. Draw main pattern of Langer's lines.
      - c. Describe the horizontal and vertical divisions of face into thirds.
      - d. Describe the blood supply of face and scalp such as:
        - 1. Arterial supply by named arteries
        - 2. Venous supply by named veins
        - 3. Collateral circulations and plexuses
      - e. Describe the sensory, motor and autonomic innervation of the face such as:
        - 1. Distribution of the three divisions of the V cranial nerve
        - 2. Distribution of the motor branches of III, IV, V, VI and VII
        - 3. Describe the autonomic innervation such as:
          - a) parasympathetic supply
          - b) sympathetic supply
      - f. Describe lymphatic supply of face to regional glands such as:
        - 1. Preauricular parotid glands
        - 2. Submandibular and submental
        - 3. Retropharyngeal
    - *1.2* Understand the gross anatomy of the neck.
      - a. Identify the topographical features of such things as:
        - 1. "Triangles" of the neck
        - 2. Midline cartilages
        - 3. Hyoid bone
        - 4. Sternum and its joints
        - 5. Clavicle and its joints

- b. Draw and label the main anatomical features of:
  - 1. Triangles of the neck
  - 2. Fascial compartments of the neck
- c. Describe the main features of such things as:
  - 1. Carotid sheath and contents
- d. Describe the blood supply of such things as:
  - 1. Describe the arterial supply to such things as:
    - a) skin of the neck
    - b) thyroid gland
    - c) submandibular glands
  - 2. Describe the venous drainage pathways of the neck.
    - a) anterior jugular vein
    - b) external jugular vein
    - c) interior jugular vein
    - d) thyroid veins
- e. Describe the sensory, motor, and autonomic innervation of the neck such as:
  - 1. Sensory innervation by C2-C4
  - 2. Motor innervation of the muscles by XI and ansa hypoglossi
  - 3. Autonomic secretory functions of the submandibular gland
  - 4. Humoral function of the carotid body
- f. Describe the lymphatic compartmentalization of the neck such as:
  - 1. Superficial lymphatic chain
  - 2. Deep lymphatics supplying glands in:
    - a) subparotid
    - b) jugulo-digastric
    - c) jugulo-carotid
    - d) jugulo-omohyoid
    - e) submental
    - f) submandibular
    - g) pretracheal
    - h) supraclavicular
    - i) posterior triangle
- g. Understand the importance of the left supraclavicular node in relationship to thoracic disease.

2.0 Understand the microscopic anatomy of the head and neck.

- a. Describe the microscopic features of such things as:
  - 1. Lymph node
  - 2. Thyroid
  - 3. Parathyroid
  - 4. Skin
  - 5. Carotid body

3.0 Understand the embryologic development of the head and neck.

3.1 Understand the embryologic development of the head.

- a. Explain the differentiation of structures such as:
  - 1. Premaxilla and maxilla
  - 2. Mandible
- b. Describe the derivatives of the head.
  - 1. First branchial arch
  - 2. Medial and lateral nasal processes
  - 3. Tongue

3.2 Understand the embryological development of the neck.
  a. Explain the differentiation of structures such as:
    1. Thyroid
    2. Parathyroid
    3. Thymus
  b. Decribe the derivatives from structures such as:
    1. Branchial arches
    2. Pharyngeal pouches
    3. Cervical sinus of His
    4. Branchial clefts
    5. Branchial arteries
    6. Branchial nerves

4.0 Understand the relationship of anatomical areas that are closely related to the head and neck.
  a. Describe the relationship of the carotid sheath to such things as:
    1. Fascial compartments
    2. Hyoid bone
    3. Omohyoid muscle
    4. Posterior belly of the digastric muscle
    5. Cranial nerve XII
    6. Thoracic duct
  b. Describe the relationships of the cranial nerves to each other.
  c. Describe the significance of the relationship of the fascial compartments to each other and the mediastinum.

5.0 Understand the physiology of the head and neck.

5.1 Understand the physiology of the head.
  a. Explain the actions of peripheral vasodilatation in temperature control.
  b. Describe the characteristics of sweating.

5.2 Understand the physiology of the neck.
  a. Explain action of strap muscle during respiration, phonation, swallowing and the valsalva maneuver.
  b. Describe the function of such things as:
    1. Thyroid gland
    2. Parathyroid gland
    3. Thymus
    4. Carotid bodies
    5. Lymph nodes
    6. Cervical sympathetic chain
    7. Phrenic nerve
  c. Describe the production of thyroid and parathyroid hormones.

6.0 Understand the routine tests of the head and neck.
  a. Radiological studies such as:
    1. AP and lateral views of the neck
    2. Soft tissue
    3. Skull and facial bones

7.0 Understand the special tests of the head and neck.
  a. Describe radiological tests such as:
    1. Polytomography
    2. CAT scan
    3. Contrast studies
    4. Xeroradiography

        5. Bone scan
        6. Thyroid scan
      b. Describe the electromyographic studies.
      c. Describe the tests of thyroid and parathyroid function.

B. Skills
  1.0 Perform an appropriate examination of the head and neck.
  1.1 Perform an appropriate examination of the head by such things as:
    a. Inspection
    b. Palpation
    c. Percussion
    d. Auscultation
    e. Transillumination
  1.2 Performs an appropriate examination of the neck by such things as:
    a. Inspection
    b. Palpation
    c. Range of motion testing
    d. Auscultation
  2.0 Perform an appropriate test of head and neck function.
  2.1 Perform an appropriate test of functions of the head.
    a. Demonstrate sensory distribution of the face.
    b. Demonstrate the motor function of expression mastication.
    c. Demonstrate the autonomic control of peripheral vasodilatation and sweating.
  2.2 Perform an appropriate test of neck functions.
    a. Describe the segmental cervical sensory distribution.
    b. Demonstrate the motor function of the neck muscles.

C. Attitudes
  1.0 Appreciate the need for good clinical history.
  2.0 Appreciate the significance of a good physical exam.
  3.0 Appreciate the need for special tests in evaluating such things as:
    a. Hormonal function of the thyroid and parathyroid
    b. Function of carotid body
    c. Neuromuscular coordination in relation to:
      1. Swallowing
      2. Weight bearing
      3. Respiration
      4. Coughing

II. Head and Neck (Abnormal)

  A. Knowledge (Cognitive)
    1.0 Understand the pathology of head and neck.
    1.1 Understand the pathology of the head.
      a. Describe the common lesions of head such as:
        1. Congenital
          a) facial clefts
          b) facial cysts and sinus tracts
          c) facial hypoplasia
          d) chromosomal abnormality syndromes

2. Inflammatory
    - a) cellulitis
    - b) folliculitis – acute and chronic
3. Degenerative and metabolic
    - a) aging face syndrome
    - b) senile keratosis
    - c) solar keratosis
    - d) tophi
    - e) scleroderma and other collagen disorders
    - f) allergic dermatidies
4. Traumatic
    - a) lacerations
    - b) maxillofacial trauma as described in "Nose and Paranasal Sinuses" section II. A. *1.2* a. 4 a-c.
    - c) thermal burns
    - d) caustic and chemical burns
5. Neoplastic
    - a) basal cell carcinoma
    - b) squamous cell carcinoma
    - c) melanoma
    - d) nevi
    - e) sarcomas
6. Psychophysiologic
    - a) factitious dermatitis
    - b) atypical pain
    - c) tic

1.2 Understand the pathology of the neck.

a. Describe the common lesions of the neck such as:

1. Congenital
    - a) branchial cleft cysts and sinus tracts
    - b) thyroglossal duct and cysts
    - c) dermoid
    - d) chromosomal abnormality syndromes
2. Inflammatory
    - a) deep neck infections
    - b) thyroiditis
        - 1) bacterial
        - 2) viral
        - 3) idiopathic
    - c) chronic granulomatosis infections
        - 1) T.B.
        - 2) sarcoid
        - 3) actinomycosis
3. Degenerative and metabolic
    - a) colloid goiter
    - b) torticollis
    - c) carotidynia
4. Traumatic
    - a) penetrating wounds of neck
    - b) blunt trauma to neck
    - c) lacerations and contusions
5. Neoplastic
    - a) benign
        - 1) thyroid adenoma
        - 2) parathyroid adenoma

            3) chemodectoma
            4) neurofibroma
            5) lipoma
        b) malignant
            1) primary
                (a) adenocarcinoma
                (b) lymphoma
                (c) sarcomas
                (d) basal cell carcinoma
                (e) squamous cell carcinoma
                (f) melanoma
            2) metastatic
                (a) from head and neck
                (b) from other regions
    6. Psychophysiologic
        a) tic
        b) globus phenomenon

2.0 Formulate a differential diagnosis of head and neck diseases.
    a. Prepare a differential diagnosis for chief complaints such as:
        1. Lump
        2. Pain
        3. Discharge (purulent, sanguinous, serous)
        4. Neuromuscular disorders such as:
            a) facial paralysis
            b) shoulder droop
            c) jugular foramen syndrome
        5. Fatigue and temperature intolerance
        6. Pyrexia
        7. Facial disfigurement and asymmetry
    b. Defend a differential diagnosis for chief complaints such as those listed in II. A. *2.0* a. 1-7.

3.0 Understand the use of routine tests for disorders of head and neck.

4.0 Understand the use of special tests for disorders of head and neck as listed in I. A. *7.0* a. 1-6.

5.0 Formulate a problem-solving strategy for chief complaints as described in II. A. *2.0* a. 1-7.

6.0 Formulate a management plan for diseases of head and neck.

6.1 Formulate a management plan for diseases of the head.
    a. Describe a primary treatment plan for conditions listed in II. A. *1.1* a. 1-6.
    b. Explain basis for consultation with otolaryngologist as for those listed in II. A. *1.1* a. 1-6.

6.2 Formulate a management plan for diseases of the neck.
    a. Describe a primary treatment plan for conditions listed in II. A. *1.2* a. 1-6.
    b. Explain basis for consultation with otolaryngologist as for those listed in II. A. *1.2* a. 1-6.

B. Skills

1.0 Perform an appropriate examination of the abnormal head and neck.

1.1 Perform an appropriate examination of the abnormal head.
    a. Identify abnormalities listed in II. A. *1.1* a. 1-6.
    b. Evaluate abnormalities listed in II. A. *1.1* a. 1-6.

- *1.2* Perform an appropriate examination of the abnormal neck.
    - a. Identify abnormalities listed in II. A. *1.2* a. 1-6.
    - b. Evaluate abnormalities listed in II. A. *1.2* a. 1-6.
- *2.0* Demonstrate the proper techniques for obtaining specimens.
    - a. Perform appropriate techniques for obtaining specimens for such things as:
        1. Cytology of drainage from cysts or fistulae
        2. Smear of drainage
        3. Cultures of drainage
- *3.0* Exhibit appropriate treatment skills.
    - a. Perform medical treatment for conditions such as:
        1. Uncomplicated infections of skin and subcutaneous tissues.
    - b. Perform appropriate surgical treatment for conditions such as:
        1. Small uncomplicated lacerations
        2. Jugular vein catheterization
        3. Endotracheal intubation
        4. Tracheostomy and cricothyroidotomy

C. Attitudes

- *1.0* Recognize the significance of cranio-facial and/or neck injury.
- *2.0* Instruct the patient in the care of surgically repaired traumatic injuries to the face and neck.
- *3.0* Communicate to a patient the dangers and difficulties associated with feeding when intermaxillary fixation has been applied.
- *4.0* Appreciate the need for protection of head and neck in high velocity travel or physical sports.
    - a. Discuss use of seat belts in automobile.
    - b. Explain the requirement of helmets in football, hockey, etc.

PHARYNX AND ESOPHAGUS

I. Pharynx and Esophagus (Normal)

  A. Knowledge (Cognitive)

    1.0 Understand the gross anatomy of the pharynx and esophagus.

    1.1 Understand the gross anatomy of the pharynx.

      a. Identify the topographical features such as:
        1. Oropharyngeal area
          a) faucial tonsils
          b) anterior and posterior tonsillar pillars
          c) foramen caecum
          d) posterior and lateral oropharyngeal walls
          e) soft palate
        2. Nasopharyngeal area
          a) adenoid
          b) posterior choanae
          c) torus tubarius and Eustachian tube orifices
          d) fossae of Rosenmüller
          e) nasopharyngeal vault
        3. Hypopharyngeal area
          a) valleculae
          b) lateral walls
          c) pharyngoepiglottic folds
          d) pyriform sinuses
          e) postcricoid area
          f) lingual tonsils
      b. Label and delineate boundaries of the divisions of the pharynx.
      c. Describe the external carotid artery blood supply of the pharynx.
      d. Describe the sensory, motor, and autonomic innervation of the pharynx.
        1. Pharyngeal plexus including
          a) cranial nerves IX, X
          b) parasympathetic
          c) sympathetic
        2. Cranial nerve V innervation of the tensor veli palatini.
      e. Describe the compartmentalization of the lymphatic drainage of the pharynx.

    1.2 Understand the gross anatomy of the esophagus.

      a. Describe the main anatomic features of the esophagus such as:
        1. Cricopharyngeal sphincter
        2. Cardioesophageal junction
        3. Length and direction of esophagus
      b. Describe the blood supply of the esophagus such as:
        1. Gastrohepatic
        2. Segmental perforators from the aorta and bronchial arteries
        3. Inferior thyroid artery

- c. Describe the sensory, motor, and autonomic innervation such as:
  - 1. Vagus nerve in upper 1/3
  - 2. Submucosal plexuses (Meissner's and Auerbach's) in lower 2/3's
- d. Describe the compartmentalization of the lymphatic drainage of the esophagus.

2.0 Understand the microscopic anatomy of the pharynx and esophagus.

2.1 Understand the microscopic anatomy of the pharynx.

- a. Describe the microscopic features of the pharyngeal mucosa.
- b. Describe the microscopic features of Waldeyer's ring of lymphoid tissue.

2.2 Understand the microscopic anatomy of the esophagus.

- a. Describe the microscopic features of such things as:
  - 1. Esophageal mucosa including glands
  - 2. Muscular layers of the:
    - a) upper thirds
    - b) middle thirds
    - c) lower thirds
  - 3. Auerbach's and Meissner's plexuses
- b. Label a schematic diagram of the muscular layers and the neurologic plexus in the upper, middle, and lower esophagus.

3.0 Understand the embryologic development of the pharynx.

- a. Explain the differentiation of structures such as:
  - 1. Oropharynx
    - a) soft palate
  - 2. Nasopharynx
    - a) posterior choanae
    - b) Eustachian tube orifice
  - 3. Hypopharynx
    - a) base of tongue
    - b) separation of larynx and pharynx

3.2 Understand the embryological development of the esophagus.

- a. Explain the differentiation of structures such as:
  - 1. Esophageal lumen
  - 2. Common party wall
  - 3. Diaphragmatic sphincters

4.0 Understand the relationship of major anatomic areas and structures that are closely related to the pharynx and esophagus.

4.1 Understand the relationship of major anatomic areas and structures that are closely related to the pharynx.

- a. Describe the relationship of the pharynx to such things as:
  - 1. The common boundaries of the hypopharynx with the larynx.
  - 2. The fascial planes and boundaries of the following:
    - a) peritonsillar region
    - b) lateral pharyngeal region
    - c) retropharyngeal
    - d) prevertebral spaces
    - e) parapharyngeal space
    - f) masticator space

3. Describe and locate the intrinsic and extrinsic narrowings of the esophagus by such things as:
    a) cricopharyngeus
    b) arch of aorta
    c) left bronchus
    d) cardiac sphincter

4.2 Understand the esophageal relationship to closely related anatomical areas and structures.

a. Describe the relationship of structures such as:
    1. Pyriform sinus
    2. Cricoid cartilage
    3. Right and left recurrent laryngeal nerve
    4. Carotid sheath
    5. Sympathetic chain
    6. Vagus nerve and recurrent nerves
    7. Arch of the aorta
    8. Trachea and bronchi
    9. Mediastinum compartments and contents
    10. Diaphragm
    11. Prevertebal fascia

b. Explain significance of these relationships in I. A. *4.2* a. 1-11.

c. Label diagram of cross sections of the neck and thorax at various levels.

5.0 Understand the physiology of the pharynx and esophagus.

5.1 Understand the physiology of the pharynx.

a. Explain the action of the pharyngeal structures during normal swallowing such as:
    1. Velum of soft palate
    2. Posterior pharyngeal wall
    3. Passavant's ridge
    4. Base of tongue
    5. Pharyngeal surface of epiglottis
    6. Cricopharyngeus
    7. Laryngeal structures

b. Describe the function of the pharynx in speech production such as:
    1. Velopharyngeal competence

c. Describe the role of pharyngeal lymphoid tissue in immunodefense.

5.2 Understand the physiology of the esophagus.

a. Describe the mechanism of esophageal peristalsis.

b. Explain the mechanism of vomiting.

6.0 Understand routine tests of pharynx and esophagus.

a. Describe routine tests of pharynx and esophagus such as:
    1. Culture of pharynx
    2. Barium swallow

7.0 Understand the special tests.

a. Describe specialized tests of pharynx and esophagus such as:
    1. Nasopharyngogram
    2. Cine-fluoroscopy
    3. Manometric pressures determinations

4. Esophagoscopy
    - a) inspection
    - b) biopsy

B. Skills

1.0 Perform an appropriate exam of pharynx and esophagus.

1.1 Perform an appropriate pharyngeal exam.

a. Identify by inspection using an appropriate source of illumination such things as:

1. Nasopharynx
    - a) posterior choanae
    - b) Eustachian tube orifice
    - c) adenoids
2. Oropharynx
    - a) faucial tonsils
    - b) anterior and posterior tonsillar pillars
3. Hypopharynx
    - a) base of tongue
    - b) vallecula
    - c) pyriform sinus
    - d) epiglottis

b. Identify by palpation structures such as:

1. Faucial tonsils
2. Base of tongue

1.2 Perform an appropriate test for pharyngoesophageal function.

a. Demonstrate capability to swallow liquids and solids.

b. Demonstrate velopharyngeal closure in speech.

C. Attitudes

1.0 Appreciate that the pharynx is a common food and air conduit and its implication.

II. Pharynx and Esophagus (Abnormal)

A. Knowledge (Cognitive)

1.0 Understand the pathology of pharynx and esophagus.

1.1 Understand pathology of the pharynx.

a. Describe the common lesions of the pharynx such as:

1. Congenital
    - a) velopharyngeal incompetence
    - b) lingual thyroid
    - c) Thornwaldt cyst
    - d) stenosis
    - e) glioma and encephalocele
    - f) hypopharyngeal cysts
2. Inflammatory
    - a) acute viral pharyngitis
    - b) acute bacterial pharyngitis
    - c) infectious mononucleosis
    - d) parapharyngeal and retropharyngeal abscess
    - e) peritonsillar abscess
    - f) hypertrophic tonsils and adenoids

3. Degenerative and metabolic
    - a) bulbar paralysis
    - b) neuromuscular incoordination
    - c) cervical osteophytosis
    - d) Plummer-Vinson syndrome
    - e) "sicca" syndrome
    - f) myasthenia gravis
    - g) allergic pharyngitis
    - h) angioneurotic edema
    - i) autoimmune diseases
4. Trauma
    - a) caustic injury
    - b) foreign body
    - c) lacerations
    - d) perforations
5. Neoplastic
    - a) juvenile nasopharyngeal angiofibroma
    - b) squamous cell carcinoma
    - c) lymphoma
    - d) adenocarcinoma
    - e) rhabdomyosarcoma
6. Psychophysiologic
    - a) globus phenomenon

1.2 Understand the pathology of the esophagus.

a. Describe common lesions of the esophagus.

1. Congenital
    - a) atresia with or without fistula
    - b) stenosis
    - c) webs
    - d) vascular rings
    - e) hiatal hernia
    - f) short esophagus
2. Inflammatory
    - a) granulomatous esophagitis
    - b) reflux esophagitis
3. Degenerative and metabolic
    - a) neuromuscular incoordination
    - b) autoimmune disorders
    - c) esophageal varices
    - d) diverticuli
    - e) achalasia
4. Traumatic
    - a) caustic ingestion
    - b) foreign body
    - c) laceration
    - d) perforation
    - e) Mallory-Weiss syndrome
5. Neoplastic
    - a) squamous cell carcinoma
    - b) papilloma
    - c) adenocarcinoma
6. Psychophysiologic
    - a) dysphagia

- *2.0* Formulate a differential diagnosis.
  - a. Prepare a differential diagnosis for chief complaints such as:
    1. Sore throat
    2. Dysphagia
    3. Odynophagia
    4. Lump in throat
    5. Retrosternal pain
    6. Unilateral hearing loss
    7. Nasal obstruction
    8. Emesis and hematemesis
    9. Aspiration
    10. Rhinolalia
  - b. Defend a differential diagnosis for chief complaints as those listed in II. A. *2.0* a. 1-10.
- *3.0* Understand the use of routine tests for evaluation of disorders of the pharynx and esophagus.
  - a. Describe routine tests such as:
    1. Culture
    2. Barium swallow
  - b. Discuss the indications for the routine tests listed in I. A. *6.0* a. 1-2.
- *4.0* Understand the use of special tests for evaluation of disorders of the pharynx and esophagus.
  - a. Describe the principles of special tests such as:
    1. Those listed in I. A. *7.0* a. 1-4.
    2. Carotid angiography
    3. Aortogram
    4. Speech evaluation
  - b. Discuss the indications of special tests for such things as those listed in II. A. *4.0* a. 1-4.
- *5.0* Formulate a problem-solving strategy for chief complaints as described in II. A. *2.0* a. 1-11.
- *6.0* Formulate a management plan for diseases of the pharynx and esophagus.
  - a. Describe a treatment plan for conditions such as those listed in II. A. *1.1* and *1.2*.
  - b. Explain the basis for consultation and referral with an otolaryngologist for conditions listed in II. A. *1.1* and *1.2*.

B. Skills

- *1.0* Perform the appropriate exam of the abnormal pharynx and esophagus.
- *1.1* Perform an appropriate exam of the abnormal pharynx.
  - a. Identify by inspection using an appropriate source of illumination abnormalities such as:
    1. Nasopharyngeal lesion
    2. Hypertrophic adenoids
    3. Hypertrophic tonsillitis
    4. Peritonsillar abscess
    5. Retropharyngeal abscess
    6. Lingual thyroid
    7. Hypopharyngeal cysts
    8. Foreign body

        9. Carcinoma of pharynx
        10. Pharyngeal inflammatory lesions
    b. Identify by palpation, or other means, such abnormalities as:
        1. Choanal atresia
        2. Nasopharyngeal stenosis
        3. Halitosis
    c. Evaluate abnormalities described in II. B. *1.1* a. 1-10.

1.2 Perform an appropriate examination of the abnormal esophagus.
    a. Not applicable

2.0 Demonstrate the proper techniques for obtaining specimens.
    a. Perform appropriate technique for obtaining pharyngeal cultures.

3.0 Exhibit appropriate treatment skills.
    a. Perform appropriate medical treatment procedures for those listed in II. A. *1.1* and *1.2*.
    b. Perform appropriate surgical treatment procedures.
        1. Not applicable

C. Attitudes

1.0 Appreciate the significance of aspiration from rupture of pharyngeal tissues.

2.0 Recognize that disorders of the pharynx may disturb respiration, speech, and deglutition.

3.0 Realize the social embarrassment of major airway and food passage disturbances.

4.0 Realize the contagious nature of some pharyngeal infections and their systemic complications.

NOSE AND PARANASAL SINUSES

- I. Nose and Paranasal Sinuses (Normal)
  - A. Knowledge (Cognitive)
    - *1.0* Understand the gross anatomy of nose and paranasal sinuses.
    - *1.1* Understand gross anatomy of the nose.
      - a. Identify the topographical features such as:
        - 1. Bone and cartilages of external nose
          - a) nasal bones
          - b) upper lateral cartilages
          - c) lower lateral cartilages
        - 2. Cartilages of the nasal tip and nares
          - a) septal cartilage
          - b) the dome, i.e., medial and lateral crura of lower lateral cartilage
          - c) anterior nasal spine
        - 3. The parts of the nasal bridge including:
          - a) glabella
          - b) nasion
          - c) nasofrontal angle
          - d) nasolabial angle
        - 4. Bones and cartilages of the nasal septum such as:
          - a) vomer
          - b) perpendicular plate of ethmoid bone
          - c) septal cartilage
          - d) premaxilla
          - e) nasal crest of palatine bone
        - 5. The three turbinates
        - 6. The location of the sinus ostia in the:
          - a) bulla ethmoiditis
          - b) sphenoethmoidal recess
          - c) nasofrontal duct
          - d) nasolacrimal duct – lacrimal sac
          - e) hiatus semilunaris
          - f) ethmoidal infundibulum
      - b. Draw and label the gross anatomic features of the external nose.
      - c. Describe the blood supply of the nose including the:
        - 1. External carotid
          - a) maxillary artery branches
          - b) facial artery branches
        - 2. Internal carotid
          - a) ophthalmic division
            - 1) anterior ethmoidal artery
            - 2) posterior ethmoidal artery
      - d. Describe the nerve supply of the nose, including the:
        - 1. Ophthalmic division of V
        - 2. Maxillary division of V
        - 3. Special sensory – olfactory nerve

    4. Autonomic nerves
        a) sympathetic nerves – deep petrosal nerve
        b) parasympathetic nerves – greater superficial petrosal nerve
    5. Facial nerve VII
  e. Describe lymphatic drainage of nose to regional glands.

1.2 Understand the gross anatomy of the paranasal sinuses.
  a. Identify topography features of the paranasal sinuses such as:
    1. Maxillary sinuses
    2. Ethmoidal sinuses
    3. Frontal sinuses
    4. Sphenoidal sinuses
  b. Draw and label the anatomic boundaries (the walls of) each paranasal sinus.
  c. Describe sensory innervation of the sinuses.
  d. Describe the location of the paranasal sinuses.
  e. Describe the arterial and venous supply for each paranasal sinus.
    1. Identify those sinuses whose venous drainage is central, i.e., towards the CNS
    2. Identify those sinuses which have some blood supply from internal carotid branches.
  f. Describe the lymphatic drainage of the sinuses to regional glands.

2.0 Understand the microscopic anatomy of the nose and paranasal sinuses.

2.1 Understand the microscopic anatomy of the nose.
  a. Describe the features of respiratory epithelium.
  b. Describe the features of olfactory epithelium.
  c. Label diagram of cross-section of respiratory epithelium.

2.2 Understand the microscopic anatomy of the sinuses.
  a. Describe the features of sinus epithelium-respiratory.
  b. Describe the relation of the cilia to the sinus ostia.
  c. Describe the characteristic features of goblet cells.

3.0 Understand the embryological development of the nose and paranasal sinuses.

3.1 Understand the embryologic development of the nose.
  a. Explain the differentiation of structures such as:
    1. Anterior nares
    2. Posterior choanae
    3. Premaxilla
    4. Nasolabial folds
    5. Floor of the nose
    6. Turbinates
    7. Olfactory epithelium
  b. Describe the origins of structures such as:
    1. Posterior choanae
    2. Nasal cavities – (nasal pit and placode)
    3. Floor of nose – palate
    4. Olfactory epithelium
    5. Turbinates – agar nasi
    6. Nasofrontal duct
    7. First branchial arch

3.2 Understand the embryology of the paranasal sinuses.
- a. Explain the process of development of a sinus.
- b. Describe the chronologic sequence of the paranasal sinuses.

4.0 Understand the relationship of anatomical areas that are closely related to the nose and paranasal sinuses.

4.1 Understand the relationship of anatomical areas that are closely related to the nose.
- a. Describe the extracranial relationship of the nose and nasal cavities to such things as:
  1. Palate
  2. Nasopharynx
  3. Sinuses
  4. Orbital cavity
- b. Describe the intracranial relationship of the nose and nasal cavities to such things as:
  1. Cribriform plate
  2. Anterior fossa

4.2 Understand the relationship of anatomical areas that are closely related to the paranasal sinuses.
- a. Describe the anatomic relationships of the maxillary paranasal sinus to vital anatomic areas such as:
  1. Pterygomaxillary space
  2. Orbital floor
  3. V_2 nerve
  4. Lateral nasal wall
  5. Teeth
- b. Describe the anatomic relationships of the ethmoid sinuses to vital anatomic areas such as:
  1. Lamina papyracea
  2. Anterior wall of sphenoid
  3. Cribriform plate
  4. Middle turbinate
  5. Uncinate process
  6. Frontal sinus
- c. Describe the anatomic relationships of the sphenoid sinus to vital anatomic areas such as:
  1. Optic nerve
  2. Sella turcica
  3. Posterior ethmoid air cells
  4. Nasal septum – perpendicular plate of ethmoid bone
- d. Describe the anatomic relationships of the frontal sinuses to vital anatomic areas such as:
  1. Frontal lobes of CNS
  2. Ethmoid sinuses
  3. Cribriform plate
  4. Roof of the orbit
  5. Superior oblique eye muscle

5.0 Understand the physiology of the nose and paranasal sinuses.
- a. Explain the actions of the neurovascular supply of the nasal mucosa in monitoring:
  1. Nasal temperature, i.e., heat exchange
  2. Humidity
  3. Nasal airway patency

b. Describe the function of the nose in such things as:
  1. Speech production
  2. Olfaction
  3. Respiration in relation to the:
    a) upper airway
    b) lower airway

c. Describe the production of nasal mucus, and the protection afforded by:
  1. The filtering mechanisms of the mucus blanket
  2. Propulsive force of cilia
  3. Mucus constituents
    a) pH
    b) glycoproteins
    c) lysozyme
    d) secretory immunoglobulins

6.0 Understand routine tests of the nose and paranasal sinuses.

6.1 Understand routine test of nasal function.

a. Explain tests for nasal respiration such as:
  1. Nasal air flow – condensation test
  2. Catheter test for choanal atresia

b. Explain tests of olfaction such as:
  1. Odor identification
  2. Differentiation between odor testing and nasal sensation

c. Explain routine tests of speech such as:
  1. Listen for velopharyngeal incompetence
  2. Listen for nasal emission (denasality)
  3. Listen for nasal occlusion (hypernasality)

6.2 Understand routine tests of the paranasal sinuses.

a. Explain routine tests such as:
  1. Sinus palpation
  2. Sinus percussion
  3. Transillumination

7.0 Understand special tests of nose and paranasal sinuses.

7.1 Understand special tests of the nose.

a. Explain tests of nasal respiration such as:
  1. Nasal respirometry – flow and resistance
  2. Relationship to total airway resistance
  3. Measurement of dead space
  4. Relationship of nasal function to arterial O_2 and CO_2

b. Describe tests of olfaction such as:
  1. Odor testing (sniffing)
  2. Minimal perception of odor

c. Describe tests of speech such as:
  1. Tape recorded tests of velopharyngeal incompetence
  2. Tape recorded tests of nasal emission
  3. Radiographic tests of speech

7.2 Understand special tests of the paranasal sinuses.

a. Explain special tests such as:
  1. X-rays and tomograms of the paranasal sinuses
  2. Maxillary antrum irrigation

B. Skills
  1.1 Perform an appropriate nasal exam.
    a. Identify by inspection – using an appropriate source of illumination such things as:
      1. The symmetry of the nose and its relationship to the face.
      2. The actions of extrinsic muscles of expression on the nose, i.e., VII nerve function
      3. The patency of the nasal airways
        a) nasal septum
        b) turbinates
        c) posterior choanal
        d) floor of the nose
        e) symmetry of the nares
    b. Identify by palpation structures such as:
      1. Glabella
      2. Nasofrontal angle
      3. Nasal dorsum
      4. Nasal tip
      5. Nasolabial angle
      6. Premaxilla
      7. Ascending process of maxilla
      8. Malar eminence
      9. Inner canthus of the eye
    c. Identify the presence of normal sensory, motor, and special sensory functions by such things as:
  1.2 Perform an appropriate sinus examination.
    a. Identify by inspection – using an appropriate source of illumination such things as:
      1. Lateral nasal wall, turbinates, septum
      2. Symmetry of the face
      3. The upper gingivobuccal sulcus
      4. Region of inner canthal ligament
      5. Malar eminence
      6. Nasal airway
    b. Identify by palpation and percussion such things as:
      1. Anterior maxillary sinus wall
      2. Anterior ethmoid sinuses
      3. Frontal sinuses
    c. Evaluate the sinuses by transillumination.

C. Attitudes
  1.0 Appreciate need for adjusting climatic conditions for good nasal function.

II. Nose and Paranasal Sinuses (Abnormal)
  A. Knowledge (Cognitive)
    1.0 Understand the pathology (etiology, pathophysiology, and natural history) of nose and paranasal sinuses.
    1.1 Understand the pathology, etiology, pathophysiology, and natural history) of nasal diseases.
      a. Describe the common lesions of the nose such as:
        1. Congenital
          a) choanal atresia
          b) cleft lip and palate in relation to nose

      c) midline nasal cleft
      d) floating premaxilla, i.e., bilateral cleft lip and palate
      e) facial cleft
   2. Inflammatory
      a) vasomotor rhinitis
      b) allergic rhinitis
      c) bacterial and viral rhinitis
      d) rhinitis medicamentosa
   3. Degenerative and metabolic influences such as:
      a) atrophic rhinitis
      b) diabetes
      c) hypothyroidism
      d) pregnancy – granuloma
      e) menses
      e) emotions
      g) cystic fibrosis
   4. Traumatic
      a) epistaxis
      b) rhinolith and foreign bodies
      c) nasal fractures and deformity
      d) septal hematoma
      e) nasal septal perforation
      f) lacerations
      g) chemical inhalants
   5. Neoplastic
      a) basal cell carcinoma
      b) squamous cell carcinoma
      c) inverting papilloma
      d) melanoma
      e) nasal polyps
   6. Psychosomatic
      a) septal perforation (self-inflicted)
      b) rhinitis medicamentosa
      c) foreign body
      d) cosmetic malformation

1.2 Understand the pathology (etiology, pathophysiology and natural history) of sinus disease.

a. Describe the common lesions of sinuses such as:
   1. Congenital
      a) agenesis, i.e., frontal sinus
      b) hypoplasia, i.e., maxillary sinus
      c) Kartagener's syndrome
   2. Inflammatory
      a) acute sinusitis – bacterial and viral
      b) chronic sinusitis
      c) allergic sinusitis
      d) polypoid degeneration and mucocele formation
      e) cellulitis, abscesses, meningitis, cavernous thrombosis
   3. Degenerative and metabolic
      a) diabetes mellitus
      b) cystic fibrosis
      c) hypothyroidism

        4. Traumatic
            a) fractures of frontal, ethmoid and maxillary sinuses
            b) barotraumatic sinusitis
            c) maxillofacial fractures (LeForte's I-XI, III) and zygomatic fractures
        5. Neoplastic
            a) squamous cell carcinoma
            b) melanoma
            c) monostotic fibrous dysplasia
            d) sarcoma
            e) polypoid degeneration
        6. Psychosomatic diseases such as facial pain

2.0 Formulate a differential diagnosis.
    a. Prepare a differential diagnosis for chief complaints such as:
        1. Epistaxis, i.e., anterior, superior and posterior
        2. Nasal stuffiness
        3. Unilateral nasal obstruction
        4. Anosmia
        5. Facial pain at different locations
        6. Nasal mass
        7. Nasal drainage anterior and posterior
        8. Sneezing
        9. Cosmetic malformation, trauma, crepitation, ecchymosis, edema
        10. Facial swelling
        11. Protrusion and displacement of the eyes
        12. Anesthesia in distribution of trigeminal nerves
    b. Defend a differential diagnosis for conditions listed in II. A. *2.0* a. 1-12.

3.0 Understand the use of routine tests for evaluation of disorders of the nose and paranasal sinuses.
    a. Discuss routine tests such as:
        1. Olfaction testing (cranial nerve I)
        2. Nasal sensory testing (cranial nerve V)
        3. Sinus transillumination
    b. Explain indications for ordering or conducting tests such as those listed in II. A. *3.0* a. 1-3.
    c. Interpret results of routine tests such as those listed in II A. *3.0* a. 1-3.

4.0 Understand the use of special tests for evaluation of disorders of the nose and paranasal sinuses.
    a. Discuss radiographic analyses such as:
        1. Sinus x-rays
        2. Skull x-rays
        3. Polytomography
        4. Angiography and venography
    b. Discuss laboratory tests such as:
        1. CBC
        2. UA
        3. Coagulation tests
        4. FTA
        5. FBS-BTT

      6. Thyroid profile
      7. Culture and sensitivity
      8. Nasal smear for eosinophil counts

5.0 Formulate a problem solving strategy for chief complaints as described in II. A. *2.0* a. 1-12.

6.0 Formulate a management plan for diseases of the nose and paranasal sinuses.

   a. Explain a treatment plan for conditions such as those listed in II. A. *3.0* a. 1-3.

   b. Explain basis for consultation or referral with an otolaryngologist listed in II. A. *1.1* and *1.2*.

B. Skills

1.0 Perform an appropriate examination of the nose and paranasal sinuses using head mirror or other illumination.

1.1 Perform an appropriate examination of an abnormal nose.

   a. Identify abnormalities of the external nose such as:
      1. Cosmetic deformity of nasal tip and nasal dorsum
      2. Collapsed nasal dorsum
      3. Asymmetry of the nares
      4. Swelling, masses, erythema, and edema of the nose
      5. Nasal crepitation and abnormal motion

   b. Identify abnormalities of the internal nose such as:
      1. Bony and cartilaginous occlusion
      2. Purulent discharge and sight of origin
      3. Epistaxis
      4. Mass lesions of nasal cavities
         a) neoplasms
         b) vascular lesions
         c) polyps
      5. Choanal atresia
      6. Meatal stenosis
      7. Foreign body
      8. Visualization of mass in nasopharynx
      9. Abnormalities – soft palatal motion
      10. Nasoseptal perforations
      11. CSF rhinorrhea
      12. Mucous rhinorrhea

1.2 Perform an appropriate examination of abnormal sinuses.

   a. Identify abnormalities of the sinuses such as:
      1. Swelling of the face
         a) inner canthal area
         b) forehead, eyebrow, and eyelids
         c) malar eminence and cheek
      2. Erythema and edema of face
      3. Swelling in upper gingivobuccal sulcus
      4. Loose dentition
      5. Ulceration or lesion in palate
      6. Mass in lateral nasal wall
         a) polyps
         b) tumors

7. Purulent drainage
    a) under middle turbinate
    b) posterior superior nasal cavity
    c) nasofrontal area
    d) hiatus semilunaris
8. Progressive proptosis of eyes
9. Progressive hypertelorism

2.0 Demonstrate the proper procedures for obtaining specimens.
- a. Perform appropriate techniques for obtaining specimens for culture and sensitivity.
- b. Perform nasal smear for eosinophil and WBC counts.

3.0 Demonstrate appropriate treatments.
- a. Perform appropriate medical treatment for conditions such as:
    1. Acute uncomplicated infections of nose and sinuses
    2. Uncomplicated barotraumatic sinusitis
    3. Uncomplicated vasomotor rhinitis
    4. Uncomplicated allergic rhinitis
- b. Perform appropriate surgical treatment such as:
    1. Foreign body removal
    2. Arrest of anterior epistaxis
    3. Proetz displacements for sinusitis

C. Attitudes

1.0 Appreciate significance of early recognition of nasal airway obstruction in infancy.

2.0 Appreciate the need for early recognition and specific management of sinus trauma.
- a. Describe areas of potential septic spread.
- b. Describe complications sometimes ignored such as:
    1. CSF rhinorrhea
    2. Hypertelorism
    3. Diplopia
    4. Anosmia
    5. Trismus
    6. Cosmetic malformation, etc.

3.0 Appreciate the significance of environmental pollutants.

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COCHLEAR AND VESTIBULAR LESIONS
in
CAPSULAR OTOSCLEROSIS
as seen in
MICRODISSECTION

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COCHLEAR AND VESTIBULAR LESIONS IN CAPSULAR OTOSCLEROSIS AS SEEN IN MICRODISSECTION

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SUMMARY — In 24 temporal bones from patients with otosclerosis prepared by the method of microdissection and surface preparations, otosclerotic foci could be clearly seen during removal of the otic capsule. The state of activity of each focus was estimated on the basis of its consistency and vascularity. Small anterior foci constituted the most common form of involvement of the otic capsule. All were judged to be inactive, and none of them appeared to have caused obvious sensorineural degeneration. No cases of "pure cochlear otosclerosis" were seen. Sensorineural degeneration was associated with large anterior foci which reached the upper basal turn. One specimen displayed a circumscribed sensorineural degeneration in the upper basal turn, with an almost exact correspondence between the location and extent of the cochlear lesion and the site of invasion by the otosclerotic process in the bone and endosteum bordering on scala media and scala tympani. It is postulated that a toxic factor had diffused from the focus and acted directly on the organ of Corti. When multiple foci were present they were usually poorly defined. The otosclerotic process involved the round window, with new lamellar bone formation in the scala tympani of the lower half of the basal turn. The most extensive sensorineural degeneration in the entire material was seen in this group. One specimen also had severe cochlear hydrops. In three specimens large shunts were observed to connect the otosclerotic foci with the cochlear vasculature, which was severely dilated. Where otosclerosis involved the endosteum of the scala tympani, loss of vessels was observed. One specimen with extensive active capsular otosclerosis had severe sensorineural degeneration of the vestibular system. Vestibular pathology in fenestrated ears is also described. In a specimen from a patient with no caloric reaction, numerous hair cells were present in the macular organs.

A possible causal relationship between otosclerosis and sensorineural hearing loss has long been sought and is still much debated. Thorough study of his extensive material led Guild[1,2] to conclude that otosclerosis does not cause sensorineural degeneration. Most of his specimens, however, had small foci and no stapes fixation.[3] In recent years Guild's view has been largely superseded by the conviction that sensorineural impairment of hearing can occur as a result of extensive capsular otosclerosis.[4-10] Clinical interest in capsular otosclerosis has been further enhanced by indications that it can (at least to some extent) be diagnosed by radiological examination[11] and perhaps arrested by fluoride treatment.[12-16]

At present, controversy is centered mainly on the reliability and effectiveness of diagnosis and treatment. The main question at issue is: Can so-called cochlear otosclerosis cause *pure* sensorineural hearing loss without any evidence of a conductive component? If the answer is affirmative, a number of patients with progressive sensorineural hearing loss may in fact be suffering from cochlear otosclerosis, which might be arrested by fluoride treatment. This question is bound to elicit further discussion and divergence of opinions.[14] Schuknecht[17] has recently reviewed his extensive material and concluded that ". . . sensorineural hearing loss occurring in pure form without a conductive loss cannot be attributed to otosclerosis, for when the otosclerotic lesion is sufficiently severe to cause atrophy of the supporting sensory and neural structures within the cochlea, it invariably fixes the stapes." Shambaugh[12-15] and Linthicum,[16] on the other hand, have estimated that pure sensorineural hearing loss secondary to otosclerosis represents an important form of deafness.

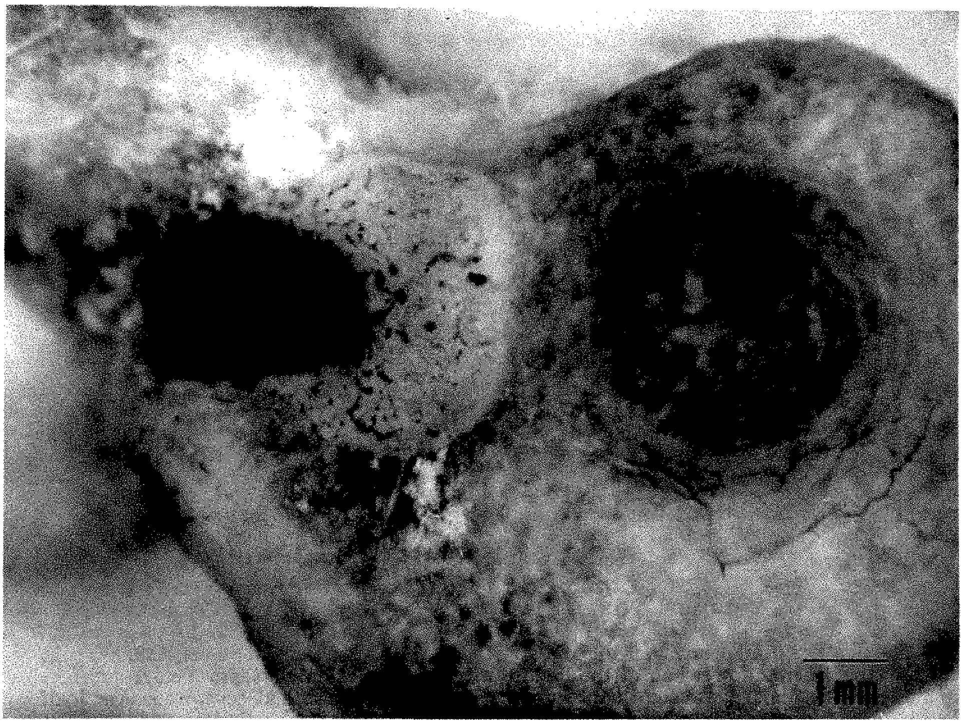

Fig. 1. Characteristic location of an anterior focus adjacent to the oval window. The focus was well-vascularized but hard, and was judged to be inactive. Blood vessels and perivascular tissue in the focus are darkly stained by OsO_4. Note the clear line of demarcation between otosclerotic and normal bone. Several more or less unstained vessels in normal capsular bone are seen below the apex (A) of the cochlea.

During this discussion a number of specific terms have evolved, of which the meaning may still be unclear to many clinicians. Hence, the following definitions should be kept in mind. "Histologic otosclerosis"[1,2] denotes the presence of an otosclerotic lesion which does not affect either the conductive or the sensory component of the hearing. "Clinical otosclerosis" refers to a reduced mobility of the stapes resulting in a conductive hearing loss. This term has been used almost interchangeably with "stapedial ankylosis" or "stapedial otosclerosis,"[12-15,17] although it seems possible that occasionally a form of stapedial otosclerosis could exist without the stapes being ankylotic; at least that must have occurred, if only temporarily, after stapes mobilization. Recently, a detailed classification of the otosclerotic involvement of the footplate has been based on examination of numerous surgical samples under the dissection microscope.[18] "Cochlear otosclerosis" or "pure cochlear otosclerosis,"[14] the focus for the present debate, implies that the otosclerotic process has involved the capsule and presumably its endosteal layer, causing sensorineural hearing loss without concomitant stapedial ankylosis. (It should be mentioned at this point that no such cases of pure cochlear otosclerosis were found in the present study.)

Strong arguments have been presented in favor of using the older term "otospongiosis," rather than "otosclerosis," as historically and histologically correct.[12-15] Although otospongiosis represents an important *phase* of the disease, it is sclerotic, hard bone that the clinician usually encounters during surgery. It was also the most common form of the disease, vividly seen and felt during the process of microdissec-

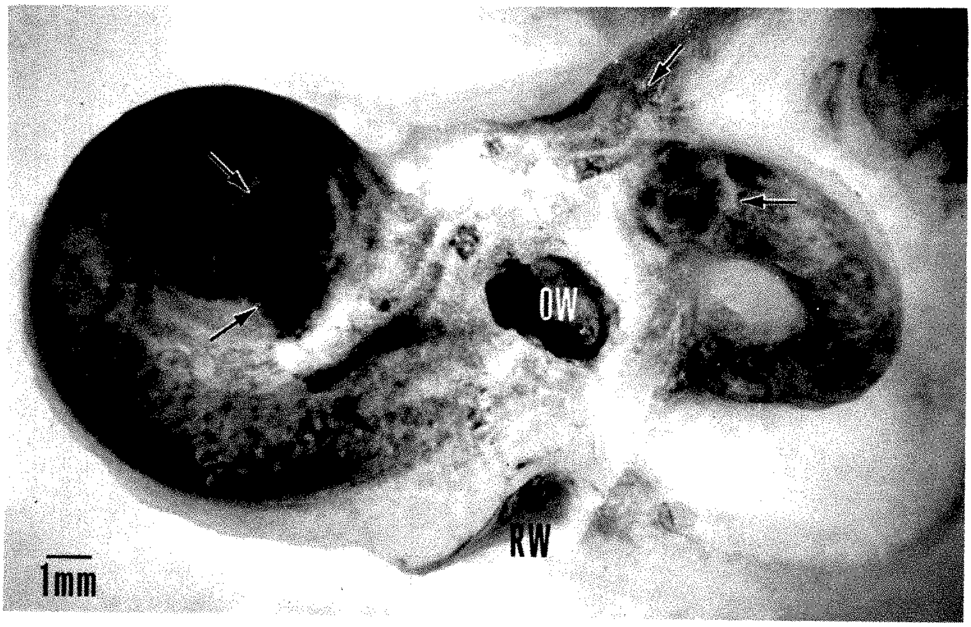

Fig. 2. (Case 1) Left ear. Large otosclerotic focus (between the two pairs of arrows), extending from the horizontal and superior bony ampullae to the apex of the cochlea. The cochlear portion of the focus was soft and highly vascular, and was judged to be active. It was darkly stained by OsO_4, penetrating the bone from the inside. OW - Oval window; RW - Round window.

tion in this study. Therefore we have continued to use the generally accepted term *otosclerosis*.

This study represents an attempt to apply the method of microdissection of the temporal bone (Figs. 1-23), lately revived by Bredberg et al[19] and Bredberg[20] and ourselves,[21,22] to the investigation of this problem. We may recall that Valsalva in the 18th century and Toynbee in the 19th both described ankylosis of the stapes on the basis of their dissections of human temporal bones.

Microdissection is admittedly not an ideal method for detailed observation of bony changes in the middle ear and labyrinth. Small foci of histologic otosclerosis could easily be overlooked, especially if located near the internal auditory canal, which is not well exposed during dissection. Nevertheless, the majority of otosclerotic foci can be clearly seen while the otic capsule is being removed, and especially after large areas of the endosteum have been exposed. The dissector can easily document the location and extent of the process, and from the texture and vascularity of the focus he can get a good idea of its state of activity (Figs. 1, 2) or inactivity (Fig. 13). The advantages of microdissection for studying the inner ear have already been pointed out.[21,22] It gives a three-dimensional view of labyrinthine anatomy and pathology, permitting a direct correlation between changes in the bone and those in the membranous labyrinth without the necessity of serial reconstruction. In this investigation we have taken advantage of the fact that surface preparations give an exceptionally fine display of the microvasculature.[23-25] Special attention has therefore been paid to cochlear vascular pathology, which has been at the focus of interest in other recent studies of this form of otosclerosis.[10]

When Wittmaack[26] published his monograph on otosclerosis, he noted that most authors agreed as to the frequent involvement of the inner ear, but disagreed as to how this occurs. Apart from the question of incidence, much the same comment could be made today. Siebenmann[27] proposed at the end of the last century that changes in the hydrostatic pressure and density of the labyrinthine fluids, membrane breaks, and possible chemical alterations in the fluids secondary to the bone disease cause changes in the organ of Corti. The latter is still accepted as a working hypothesis by many investigators, but the alterations in the inner ear fluids have yet to be clearly defined. Rüedi and Spoendlin[10] found elevated potassium and protein levels in the perilymph from patients with otosclerosis, whereas Schindler and Schnieder[28] saw no statistically verifiable difference between perilymph from otosclerotics and that from patients with unrelated diseases. Recently Chevance et al,[29,30] and Causse et al[31] found a striking correlation between the activity of hydrolytic enzymes in the perilymph and development of sensorineural hearing loss. They suggest that such enzymes play an important role in the causation of inner ear changes in otosclerosis.

Several authors[3-5,7-9] have observed atrophy and other changes of the spiral ligament and the stria vascularis adjacent to otosclerotic foci. G. T. Nager[3,9] has suggested that the sensory and neural degeneration is secondary to these atrophic changes. Linthicum[32] found in a study of 32 temporal bones that the amount of sensorineural hearing impairment was directly related to the amount of involvement of the endosteum of the spiral ligament by the otosclerotic process. Recently he and his coworkers[6,33] suggested that the otosclerotic process may distort the otic capsule or the insertion of the basilar membrane in the spiral ligament, causing a hearing loss due to a sagging of the membrane and consequently an alteration of its vibratory patterns. Schuknecht and his associates on the other hand have proposed that atrophy and shrinkage of the spiral ligament may cause tension of the basilar membrane leading to the ruptures which they have observed in a few cases with otosclerosis.[34-37]

Rüedi and Spoendlin[10] have found vascular shunts between otosclerotic foci and the venules descending in the wall of the scala tympani. They have advanced the hypothesis that the highly vascular otosclerotic focus overloads these venules with blood, causing cochlear venous congestion, vasodilatation (especially in the stria), and ischemia. These conditions in turn are thought to give rise to all of the pathological features seen in cochlear otosclerosis, including strial atrophy, sensorineural degeneration, and new lamellar bone formation in scala tympani.

Mazzoni,[38] on the basis of his study of the normal vascular anatomy of the labyrinth, has proposed a hypothesis founded on just the opposite principle. He observed that both the internal auditory artery and the radiating arterioles in the cochlea give off branches to the surrounding bone. He suggests that an active otosclerotic focus could reduce the blood supply to the inner ear by robbing the labyrinth of blood by way of the osseous branches.

In contrast to the extensive and contradictory literature and debate about cochlear pathology and audiometric changes in capsular otosclerosis, information about accompanying vestibular pathology and its clinical manifestations remains relatively sparse. The association of dizziness and vertigo with otosclerosis was, however, well recognized in the older German literature. The very first case of otosclerosis published by Siebenmann[27] in 1899 was a patient who had attacks of vertigo reminiscent of Menière's disease. One can not avoid the impression that early in this century dizziness and vertigo were considered an integral part of the clinical picture in otosclerosis. Wittmaack[26] apparently felt compelled to point out that in his experience vertigo is by no means a regular phenomenon of the otosclerotic process. At least two basic explanations were offered for the dysequilibrium when it occurred: an increased labyrinthine pressure[26,27] or a direct effect of the otosclerotic process on the vestibular nerve, particularly at the cribriform area.[39,40] In the first color plate in his 1919 monograph, Wittmaack[26] depicted a case of extensive capsular otosclerosis and severe hydrops labyrinthi. He opposed the concept that the otosclerotic process acts on the vestibular nerve and stated firmly that dizziness in otosclerosis is caused by increased secretion of inner ear fluids or possibly by alterations in the composition of the fluids, the former creating increased fluid pressure and "hydrops labyrinthi," the latter degeneration of the neuroepithelium. In his final work, the monograph published in 1955,[41] Wittmaack elaborated on the concept of pressure changes. He states that "chronische Reizhydrops" (chronic irritation hydrops) is common in extensive capsular otosclerosis. (Incidentally, the temporal bone he describes as most characteristic had extensive capsular otosclerosis, but no involvement of the stapes.) Furthermore, he goes so far as to refer to animal experiments in which he created hydrops labyrinthi by placing calcium chloride crystals on the round window membrane. On the basis of these experiments he suggests that otosclerosis may increase the concentration of calcium ions by freeing calcium from the otic capsule and thus causing hydrops.

Since the publication of these interesting cases and the rather imaginative discussions which took place for the most part half a century ago, little has been added to our knowledge about vestibular pathology in otosclerosis. The incidence of hydrops labyrinthi associated with otosclerosis appears to be very low in present investigations. Schuknecht* in his large material has only one pair of temporal bones from a patient who had Menière's disease combined with otosclerosis. The patient had bilateral hydrops with a small unilateral anterior focus causing stapes ankylosis. The focus did not reach the endosteum, and the finding of otosclerosis was considered purely coincidental. Black et al[42] have published one case of Menière's disease in which histology revealed hydrops in both ears and multiple otosclerotic foci bilaterally. Recently Sando et al[43] published two cases, one associated with dizziness and one with "blackouts." Both patients had severe degeneration of the superior branch of the vestibular nerve. Like the old German investigators before them, they attributed this to encroachment by the otosclerotic focus upon the bone immediately adjacent to the nerve at the cribriform plate. Gussen[44] has described a case of otosclerosis associated with focal degeneration of the maculae and cristae.

From a review of the literature about the clinical manifestations of dysequilibrium in otosclerosis patients it appears that one can distinguish two groups of patients, viz, those with Menière's disease or attacks reminiscent of the disease[12,45-52] and those with more unspecific types of dizziness or positional vertigo.[51-58] McCabe[59] has suggested an "otosclerotic inner ear syndrome" which may represent a third group of patients. Episodic vertigo occurs in that group, but the patients have no positional nystagmus and normal caloric response.

In the latest of the electronystagmographic studies of patients with otosclerosis, Virolainen[60] reported positional nystagmus in 33.3% and unilateral hypoexcitability in 55% of his material. This is in agreement with other vestibulometric investigations. Patients with objective vestibular disturbances showed greater hearing losses than the others, with statistically significant differences at 4000 and 6000 Hz.

In relating these clinical investigations to histopathological findings it is only natural to assume that the patients with attacks reminiscent of Menière's disease have hydrops labyrinthi, and that the patients with dizziness and postural vertigo suffer from the various forms of vestibular sensorineural degeneration mentioned earlier. However, the temporal bone material presently available is much too limited to allow any classification on a sound histopathological basis. What is cause and what is coincidental finding in otosclerotics with dysequilibrium still remains a puzzle.

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*Schuknecht HF: Personal communication.

TABLE 1. CASES WITH LABYRINTHINE PATHOLOGY CLEARLY ATTRIBUTABLE TO OTOSCLEROSIS

Case No.	*Race, Sex*	*Age*	*Side*	*Extent of Focus*	*State of Activity*	*Endosteum*	*Specific Cochlear Pathology*	*Vascular Pathology*	*Vestibular Pathology*
1	W-M	83	L	Large ant. focus extending from sup. and hor. amp. to apex (Fig. 2)	Active	Thickened	Circumscribed sensorineural degen. in basal turn, closely corresponding to area of endosteum affected by otosclerosis	Loss of vessels in scala tymp. at focus. Vasodilatation, one shunt in scala tymp. at focus (Fig. 10)	
2	W-M	61	R,L	Multiple foci along basal turn. New bone formation almost occluding scala tymp. in lower half. Otosclerosis involving sup. and hor. bony amp. and canals	Active	Thickened	Complete loss of outer hair cells. Most of inner hair cells remain. Severe nerve degen. in lower half of basal turn. Atrophy and fibrosis of spir. lig.	Severe loss of vessels in scala tymp. Devascularization also in scalae vest. and med. Vasodilatation. Shunts in scala tymp. (Fig. 10)	Severe sensorineural degen. R (Fig. 20)
3	W-M	71	R,L	Large bilat. multiple foci, bony cysts R (Fig. 14)	Active	Thickened	Bilat. severe sensorineural degen. and atrophy of spir. lig. Hydrops labyrinthi, basilar membrane defects, L (Figs. 14-16)	Two shunts of capillary size in scala tymp. (Fig. 17)	
4	W-M	62	R	Large multiple foci involving amp. and most of the cochlea	Cochlea inactive, sclerotic. Vestib. caps. partly active		Severe sensorineural degen.		Complete loss of sensory cells from all cristae (Fig. 21)

TABLE 2. CASES WITH LABYRINTHINE PATHOLOGY PROBABLY CAUSED BY OTOSCLEROSIS

Case No.	*Race, Sex*	*Age*	*Side*	*Extent of Focus*	*State of Activity*	*Endosteum*	*Specific Cochlear Pathology*	*Vascular Pathology*	*Vestibular Pathology*
5	W-M	74	R	Relatively large ant. focus, extending to upper basal turn (Fig. 11)	Inactive		Circumscribed sensorineural degen. slightly basal to lesion		Large fenestration. Collapse of vestib. memb. labyrinth. Severe degen. of all vestib. sensory epithelia (Fig. 22)
6	W-M	62	R,L	Large ant. focus	Inactive		Severe degen. of hair cells		Fenestration
7	W-M	65	R	Large multiple foci involving post. amp. and most of cochlea	Mostly inactive	Small circumscribed darkened area adjoin. and ant. to round window	Severe degen. of hair cells		Fenestration. Severe sensory cell degen. all cristae and utric.

METHODS AND MATERIALS

The material to be described forms part of a large collection of temporal bones, portions of which have already been reported.[23-25,61,62] Normal and presbyacusic material for the purpose of this study was also obtained from the same collection. A total of 24 otosclerotic bones were examined, of which 18 were obtained at autopsy in hospitals associated with the University of Michigan Medical School. In addition, six single temporal bones with otosclerosis were obtained from the Ear Research Institute in Los Angeles. In all cases the diagnosis of otosclerosis was based upon a clinical history of the disease, or upon the postmortem finding of ankylosis of the stapes, or both. All of the bones showed an ankylosed stapes, except for those from patients who had undergone stapedectomy. A part of the material is summarized in Tables 1 and 2.

The temporal bones were processed according to the method that we have previously outlined.[21] The method is described in detail elsewhere.[22] The middle ear is routinely explored under the Zeiss operating microscope and the mobility of the stapes carefully examined with middle ear instruments. The patency of the round window and the extent of possible round window otosclerosis are evaluated by inspection and probing of the window niche and membrane. In cases of otosclerosis a reliable evaluation of the degree of occlusion can not be made until the scala tympani has been opened. The stapes (or in cases of stapedectomized specimens, the prosthesis) is removed and the round window membrane is carefully perforated at its lower margin. Thus a "clinical" evaluation of possible otosclerosis in both windows can be made before the actual dissection. The inner ear is then fixed and stained in the usual way with repeated perilymphatic perfusions of 1% osmium tetroxide injected through the oval window. Staining time is kept short, i.e., approximately 4-5 minutes, counting from the first OsO_4-perfusion. After the otic capsule has been reduced to a thin shell by means of dental burrs and then carefully removed, the membranous labyrinth is dissected under alcohol into surface preparations.

During the initial perfusion it is important to make certain that there is a good circulation of the fixative-stain. This is done by applying suction at the round window niche with a finely-drawn pipet and observing whether the fluid level is lowered in the vestibule. Failure to achieve circulation despite a proper perforation of the round window membrane usually means that the scala tympani is occluded. Occlusion may be caused by internal otitis with exudate in the scalae, by cochlear hemorrhage, or by otosclerosis obturating the scala tympani or the round window. (Intralabyrinthine bleedings are common in patients with leukemia. Blood clots can also sometimes be forced into the cochlea during the perfusion.)

If the round window is visibly occluded by otosclerosis or if no circulation is achieved, a minute hole is drilled in the scala tympani in the lower half of the basal turn (Fig. 16). This usually enables the investigator to complete a successful perilymphatic perfusion of the cochlea, using the drill hole as outlet for the fluid.

All microdissections are photographed under the Wild-Heerbrugg M-5 Stereomicroscope, with the specimen immersed in 70% alcohol. In selected cases the hair cell population of the cristae and maculae is photographed with the scanning electron microscope.

Four bones (Cases 2 and 3) were decalcified after dissection was completed, and the remaining tissue was embedded and sectioned. There were no additional findings of importance in these specimens that would justify discussion here. The new bone in the scala tympani was of the lamellar type.

RESULTS

ACTIVITY OF FOCI

Otosclerotic foci are easily distinguished from normal capsular bone because of their different texture and color (Figs. 1, 2, 11, 13). In addition, an otosclerotic focus, even when it is not soft, may be stained to some extent by OsO_4 because it is more porous and apparently contains more organic material than normal capsular bone (Fig. 2). The blood vessels and the perivascular tissue stain easily and appear as black dots and irregular black strands (Fig. 1). In ten of the bones, most of the foci had a coarse, "sugary" texture with varying degrees of vascularity, oftentimes greater than that of the surrounding normal bone. The best-vascularized focus in this group is pictured in Figure 1. These bones were considered to represent a postspongiotic phase. In nine other temporal bones the foci were hard, smooth, whitish, and obviously sclerotic, with few or no blood vessels visible (Figs. 11, 13). Both of these types of otosclerotic process were termed "inactive" in this study. This classification is admittedly relative and somewhat arbitrary; it is based on the fact that all of them were completely solid.

Only in five cases (1, 2, 3, 4, 7, Tables 1, 2) was the otosclerotic process classified as "active" or "partly active." Foci of this third type were darkly-stained, soft, and highly vascularized. They clearly represented the spongiotic state

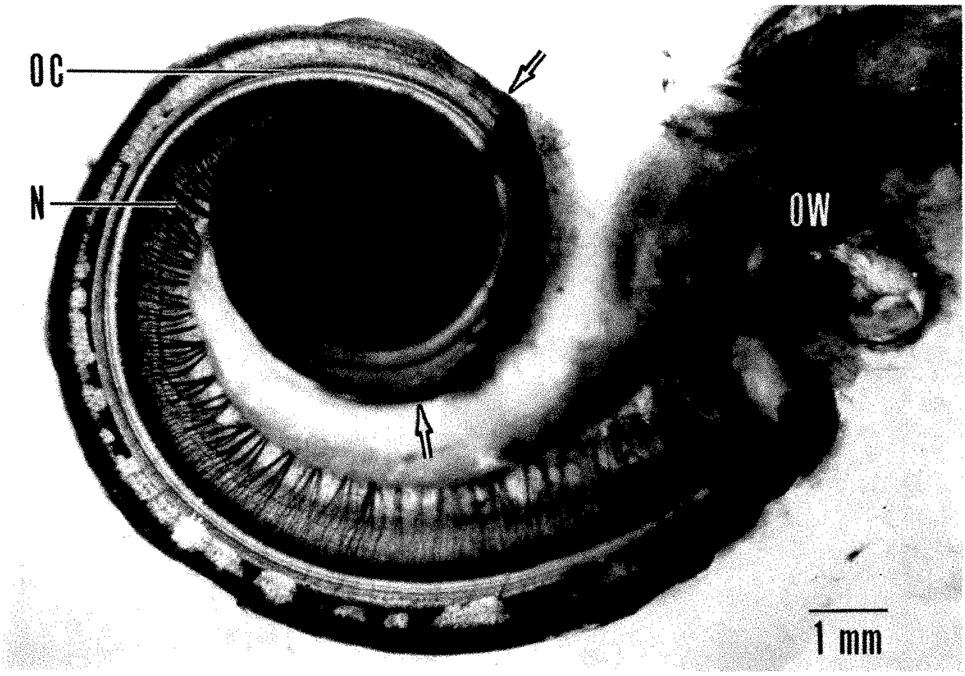

Fig. 3. Same ear as in Fig. 2, with most of the otic capsule removed and the spiral ligament dissected away. Note the darkly-stained portion of the focus in the upper basal turn, especially that in the scala tympani seen through the translucent basilar membrane. Arrows indicate the longitudinal extent of the lesion. Organ of Corti (OC) is seen as two dark bands representing the inner and outer hair cells separated by the tunnel. N - Network of myelinated radial and intralaminar spiral nerve fibers. OW - Oval window, with part of the ankylosed footplate still in situ. Nerve degeneration, characteristic of presbyacusis, is visible in the lower basal turn.

(Fig. 2). These bones will be described in greater detail below. In one bone no focus was found, despite the fact that the patient had undergone both fenestration and stapedectomy in that ear for clinical otosclerosis. In another pair of bones the otosclerosis involved only the stapes and the margin of the oval window.

GENERAL LABYRINTHINE PATHOLOGY NOT RELATED TO OTOSCLEROSIS

With aging, numerous changes take place in the labyrinth, including various forms of vascular pathology, strial atrophy, and sensorineural degeneration, which we have described in previous reports.[24,25,61] Most of the patients from whom our small collection of otosclerotic temporal bones was obtained were of relatively advanced age and would be expected to exhibit typical presbyacusic changes in the inner ear. Without an extensive quantitative and statistical analysis of "normal" presbyacusic material, which we have not made, it is not possible to state with certainty whether and to what extent otosclerosis enhances, for example, the characteristic hair cell loss in the lower basal turn. Neither can we tell whether stapedectomy itself may not cause some hair cell degeneration. We have therefore concerned ourselves mainly with pathology that can be clearly related to the otosclerotic process.

COCHLEAR PATHOLOGY DUE TO OTOSCLEROSIS (TABLES 1, 2)

In four temporal bones, one pair and two single bones, of which three specimens had active otosclerotic processes and one multiple but sclerotic foci, we found inner ear pathology that was clearly caused by otosclerosis. In another pair of temporal bones, Case 3,

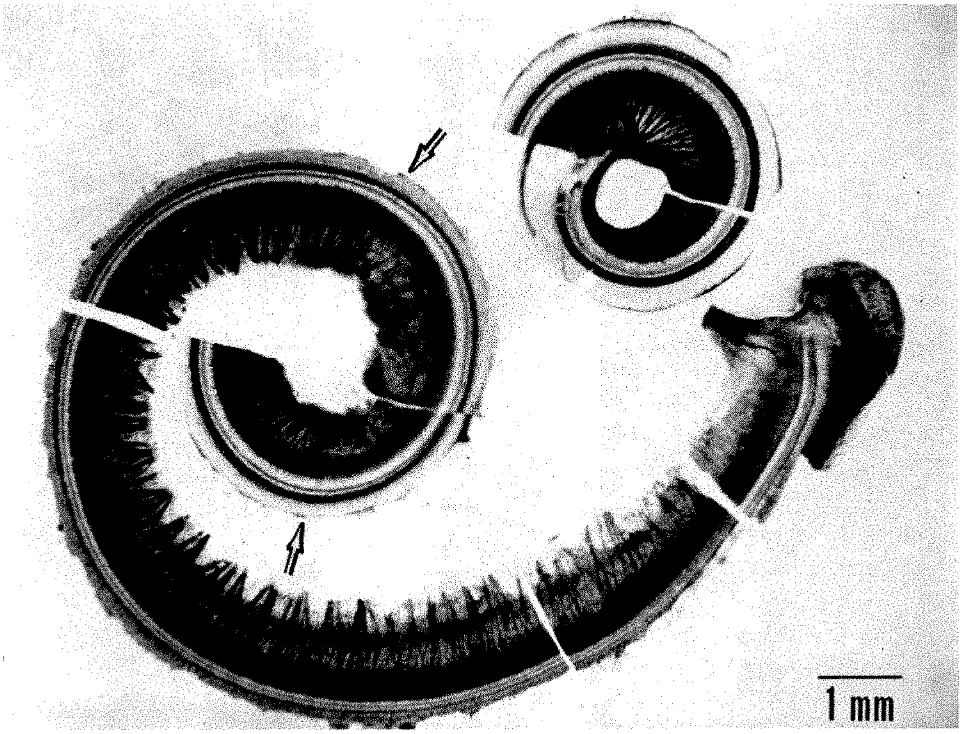

Fig. 4. Entire organ of Corti with osseous spiral lamina dissected out from the preparation in Fig. 3. Note the circumscribed nerve degeneration between the arrows, closely corresponding to the region in the scala media and scala tympani invaded by otosclerosis (cf. Figs. 2, 3, 5). The spiral has been divided along an imaginary line passing tangential to the anterior margin of the round window and through the helicotrema; the lower basal turn has been subdivided. The most basal portion still has the spiral ligament and the ductus reuniens attached to it. Note also the varying width of the basilar membrane in the various turns.[22]

there was a very severe sensorineural degeneration and extensive, partly active, capsular otosclerosis, which in all likelihood was a major cause of these changes. The causal role of the otosclerotic process was difficult to evaluate because of other diseases involved which also could have damaged the inner ear. In a seventh single bone (Case 5) with a large inactive process there was circumscribed degeneration close to the focus which could possibly have been caused by otosclerosis. In another three specimens it appeared probable that the cochlear pathology observed was secondary to extensive otosclerosis (Table 2). In the rest of the material we found no specific pathology in the membranous labyrinth which could clearly be related to otosclerosis. Otherwise, the varying degree of sensorineural degeneration seen in all of these bones was attributed to aging.

SMALL ANTERIOR FOCUS AT THE OVAL WINDOW

The material in this group* representing 11 bones was limited to specimens with foci which did not reach the middle or upper basal turn and thus correspond in size to "small" or "moderate" in Guild's[1] classification.

Several of the small anterior foci were fairly well vascularized (Fig. 1), but they were all considered inactive because the bone was hard, or at least firm. All of the bones in this group showed a relatively mild sensorineural

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*These cases not included in Tables 1 and 2.

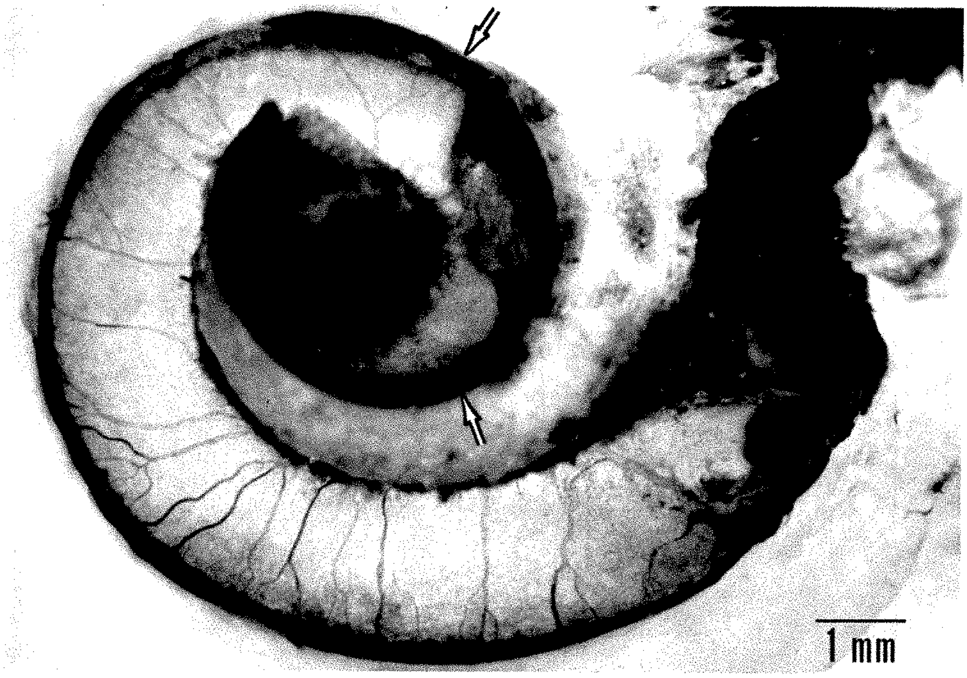

Fig. 5. Scala tympani of the same preparation as in Fig. 3, after the organ of Corti and osseous spiral lamina had been dissected away. Note the darkly-stained otosclerotic focus involving the endosteum in an area corresponding almost exactly in location and length to the region of circumscribed neural degeneration in Fig. 4. Several venules are seen taking a normal radial course toward the modiolus. Note the sharply-reduced venous drainage (confirmed by microdissection) at the otosclerotic focus.

degeneration. Because similar changes occur in our temporal bones without otosclerosis obtained from comparable age groups, and for other reasons already mentioned, it was not possible to relate the sensorineural degeneration to otosclerosis.

In the left ear from a 63-year-old female there was uneven neural degeneration in the first 5.5 mm of the osseous spiral lamina measured from the basal end, with circumscribed areas of very severe nerve degeneration extending from the base to 1.3 mm and from 3.3 mm to 4.3 mm (total length of the cochlea 29 mm). Since the patient had undergone a stapedectomy one could assume that perhaps this degeneration pattern might be characteristic of a small acoustic or hydrodynamic trauma occurring during the manipulations at the oval window.[63] A remarkably similar degeneration pattern was found in the left, unoperated ear from a 70-year-old male where an ankylotic stapes was found in the oval window. In this specimen the neural degeneration covered the first 6.6 mm, with the circumscribed areas of very severe degeneration extending from the base to 2.7 mm and from 4.9 to 5.4 mm (total length 34.8 mm). Again, similar patterns have been observed in our material with normal otic capsule, and these forms of degeneration may simply represent normal wear and tear due to aging or noise exposure.[62]

In the latter case there were extensive accumulations of concretions in the stria vascularis in the lower basal turn. We have previously described opaque, roundish concretions in association with severe strial atrophy.[24] In this case the atrophy was not of the same severity, and the concretions were translucent and embedded in the strial tissue. We have made similar observations in a few temporal bones from young individuals.

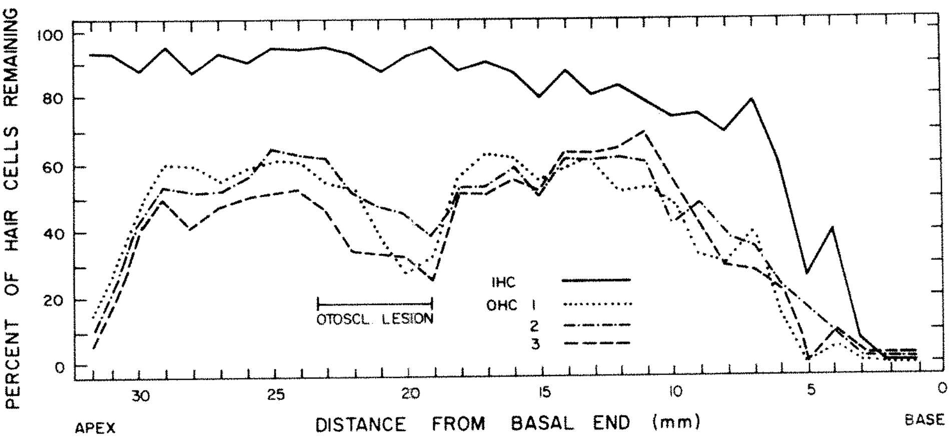

Fig. 6. (Case 1) Graph showing the distribution of the remaining hair cells along the basilar membrane in the left cochlea. Note the loss of outer hair cells at the site of the otosclerotic lesion (cf. Fig. 4). The longitudinal extent of the focus and of the region of nerve degeneration is indicated by the bar.

The finding was not considered specific for otosclerosis.

LARGE ANTERIOR FOCUS AT THE OVAL WINDOW

The foci in this group reached the upper basal turn as well as higher turns and correspond to "large" and "very large" foci in Guild's[1] terminology.

Circumscribed Sensorineural Degeneration Precisely Correlated with the Focus. The left temporal bone, Case 1, was obtained from an 83-year-old man who had undergone stapedectomy four years prior to his death (Figs. 2-10). His audiogram after surgery is shown in Figure 7. This case is the most revealing and most important in the study. A large otosclerotic focus almost surrounded the oval window and extended from the superior and horizontal bony ampullae to the apex of the cochlea (Fig. 2). The outer layers of the focus were solid, poorly vascularized, and unstained. The inner layers were soft, porous, highly vascularized, and darkly stained, because osmium tetroxide from the membranous labyrinth had penetrated and stained the soft bone. The anterior half of the focus was particularly active. The process impinged upon the three scalae in the upper basal turn and clearly involved the endosteum in the scala tympani in this area (Figs. 3, 5) but did not deform the scala tympani.

The hair cells in the cochlea were counted in surface preparations (Fig. 4) and the percentage of hair cells remaining was plotted (Fig. 6). The percentage of missing hair cells was calculated on the basis of a regular arrangement of three rows of outer hair cells. However, the pattern of hair cells in man is rather irregular, especially in the middle and apical turns, where incomplete fourth and sometimes fifth rows of outer hair cells are present.[21] Therefore, hair cell counts like those in Figure 6 are not entirely satisfactory, but they do give a fairly reliable estimate of the location and extent of hair cell loss.[62]

There was considerable sensory and neural degeneration throughout the cochlea, clearly seen in the photomicrographs and also reflected in the cytocochleogram. The degeneration pattern was characteristic of presbyacusis; the changes were most severe in the lower basal turn, and there was the typical outer hair cell loss at the apex of the cochlea.

In the upper basal turn, in an area where portions of the three scalae had been reached by active otosclerosis, there was circumscribed degeneration of outer hair cells and myelinated nerve

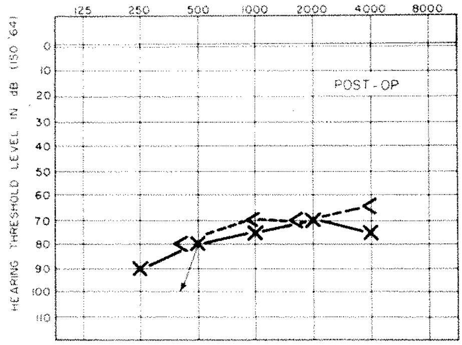

Fig. 7. (Case 1) Audiogram postop, corresponding to the temporal bone shown in Figs. 2-5. It was taken 4½ years after stapedectomy and two years before death.

fibers (Figs. 3-5). The nerve degeneration is again clearly seen in the photomicrographs, and the outer hair cell loss is mirrored in the cytocochleogram (Fig. 6). There was a close correspondence between the location and extent of this cochlear lesion and the site of invasion by the otosclerotic process in the bone and endosteum bordering on the scala media and scala tympani. The area of degeneration was in fact slightly more extensive than the bony lesion. The middle and apical turns, where active otosclerosis also reached the membranous labyrinth in the scala vestibuli and scala media but not in the scala tympani, did not display any circumscribed sensorineural degeneration.

Even where there was severe nerve degeneration most of the inner hair cells were still present. In the osseous spiral lamina the region of nerve degeneration was sharply defined, although when the specimen was examined under higher power its borders appeared less clear than they do in Figure 4. Within the area of the lesion the loss of outer hair cells was greater than on either side of it, but still incomplete. It must be remembered, however, that hair cells "present" in light microscopy may well be nonfunctional or in process of degeneration.

Vascular pathology was found throughout the cochlea. There were several dilated arterioles in the scala vestibuli. These wide arterioles gave off capillaries with very tortuous courses, some of which were also dilated (Fig. 8). Strial atrophy was present in all turns, especially in the apical half of the cochlea, but this is a common finding in specimens from elderly patients with sensorineural degeneration.[24,25] In the vicinity of the lesion the stria was thin, narrow, and in part absent; unfortunately, because of widespread strial atrophy it was not possible to ascertain if and to what extent the localized changes were directly related to the focus. Strial capillaries were severely dilated in all turns, especially in the apical half of the cochlea. This also is not an uncommon finding in elderly patients,[24,25] but the changes were much more striking than we have observed in other specimens. We did not see any specific changes in the spiral ligament at the site of the lesion. A length of the outer spiral vessel, just below the area of circumscribed degeneration, was greatly dilated (Fig. 9). The vessel was seen to take a sudden radial course and run across the basilar membrane into the spiral ligament of the scala tympani. We have not observed such dilatation of the outer spiral vessel in any of our other human preparations.

There was an almost complete loss of venous drainage in the widest portion of the focus, where the otosclerotic process reached the scala tympani in the upper basal turn (Fig. 5). Only one single, dilated venule was seen crossing the otosclerotic bone in its radial course toward the modiolus. The loss of venules was confirmed by dissecting off the endosteum overlying the focus and examining it as a surface preparation by high-power phase-contrast microscopy. Several distended venules were also seen elsewhere in the scala tympani, both basally and apically from the lesion. The vessels were particularly wide just before they entered the modiolus. Approximately in the center of the darkly-stained area of otosclerosis (Fig. 5), a large vessel, 80-90μm in diameter but without smooth muscle cells in its wall, was seen coming from inside the focus and surfacing in the scala tympani. After a short spiral

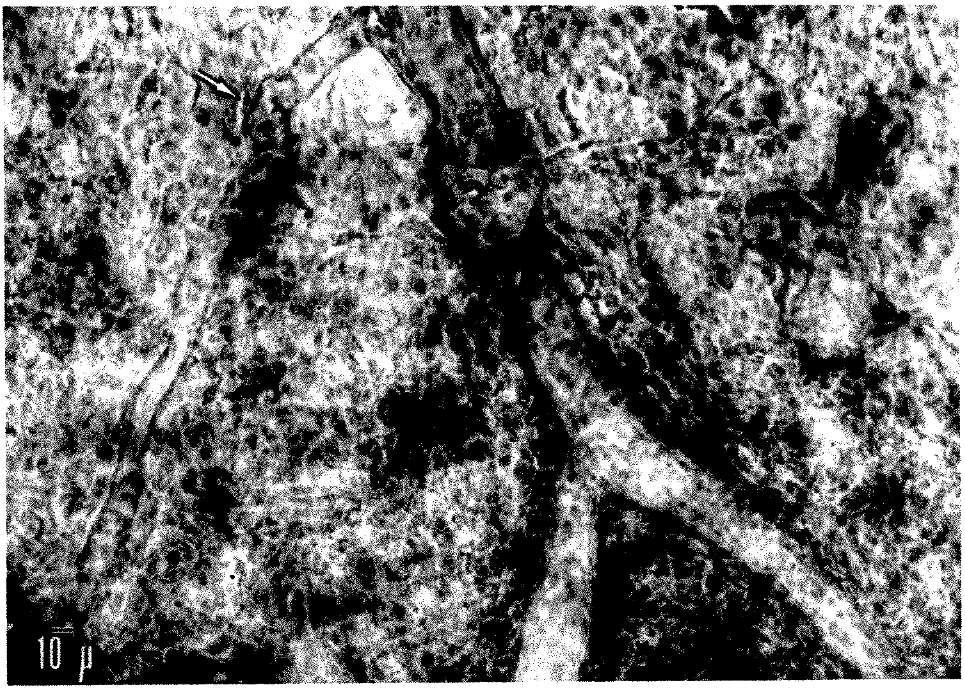

Fig. 8. (Case 1) Surface view of the spiral ligament in the scala vestibuli at the otosclerotic lesion in the left ear (cf. Fig. 3). A markedly dilated arteriole is seen giving off a distended capillary with a torturous course (arrow). Phase-contrast, OsO_4.

course basalwards the vessel turned radially and ran along the otosclerotic bone up into the spiral ligament. This vessel undoubtedly formed a connection or shunt between the otosclerotic focus and cochlear vessels in this area. We were not able to determine with certainty how the vessel was connected to the vasculature of the outer wall, nor do we know the direction of the blood flow within it. Presumably it was linked to the strial vessels, but it could also have joined the vessels of the spiral ligament or the spiral prominence, or even the outer spiral vessel (Fig. 10). This was the only shunt we found in this temporal bone, despite the fact that we were very careful in looking for new vascular connections. The endosteum lying against the otosclerotic bone in the scala tympani was markedly thickened; elsewhere in the cochlea the endosteum appeared normal.

Circumscribed Sensorineural Degeneration Adjacent to the Focus. The single right ear from Case 5 had a focus resembling the one described above, but it appeared sclerotic, nonvascular, and inactive, and it was considerably smaller (Fig. 11). It did reach very close to the scala vestibuli and scala media in the same region as in Case 1, but it was not actually in contact with the endosteum and the spiral ligament, which showed no obvious localized changes. Adjacent to the focus but extending 4-5 mm basalward from it (Fig. 12), there was a region of hair cell and nerve degeneration. Thus the correlation between the focus and this circumscribed sensorineural degeneration was by no means so precise as in Case 1. One can only speculate about the relation between the bony and the sensorineural lesions. The latter could have been a coincidental finding. In any case, its location in the upper basal turn is well above that of the lesions associated with noise exposure.[62] On the other hand, a sensorineural degeneration restricted to this region of the cochlea is exceedingly rare. We have no

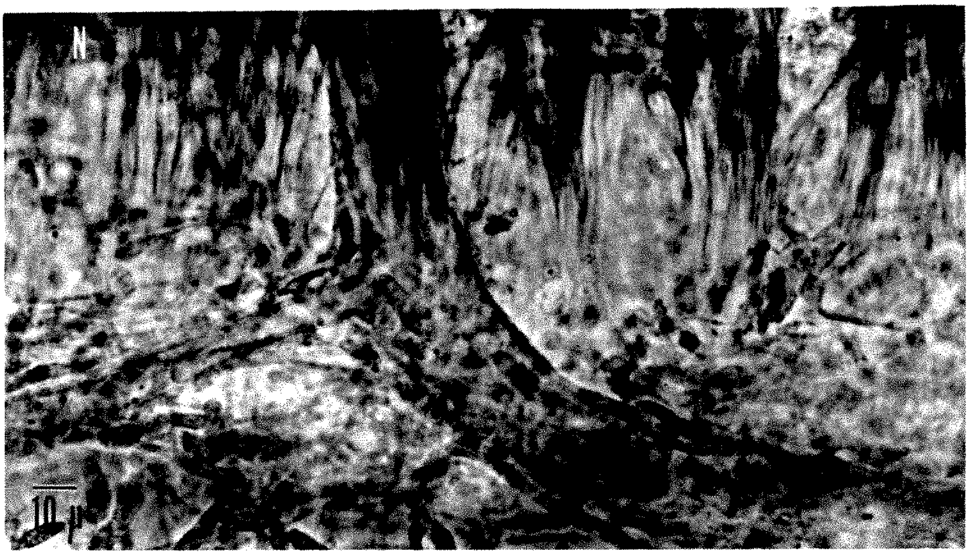

Fig. 9. Surface view of the basilar membrane at the otosclerotic lesion in Fig. 3, showing an abnormal T-junction of the outer spiral vessel. The right-hand arm and the radial limb of the T are greatly distended. Only the capillary forming the left-hand arm is of normal size. N - Cochlear nerve fibers at the habenula perforata. Phase-contrast OsO_4.

other cases with a similar degeneration pattern in our entire collection.

Sensorineural Degeneration Confined to the Lower Basal Turn. A third temporal bone* in this group, from a 70-year-old man, right side, had a focus similar in location (Fig. 13) to that just described. It was larger, but it also appeared to be inactive, sclerotic and nonvascular. It reached almost to the endosteum in the scala tympani and scala media, but there were no endosteal changes visible. No degeneration was found in this cochlea, except that in the first quadrant of the basal turn, presumably related to the patient's age.

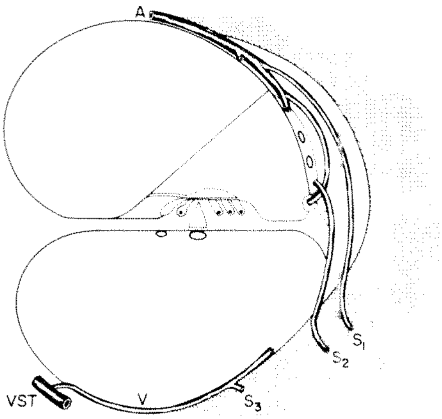

Fig. 10. Diagram showing the vascular shunts seen in five of our preparations connecting otosclerotic foci with the cochlear microvasculature. S_1 and S_2 show two probable alternative arrangements of the shunts found in four of the specimens (cf. Figs. 5 and 17). S_3 represents the multiple shunts observed in Case 2. The latter are similar to the shunts described by Rüedi and Spoendlin.[10]

A pair of temporal bones was obtained from a 68-year-old university professor, Case 6, with no history of noise exposure. The patient had had a fenestration performed on the right side about 20 years prior to his death and a stapedectomy on the left side ten years later. An audiogram had been taken a year before death. The bone conduction showed a bilateral, approximately 20 dB loss at 250 to 1000 Hz, with a steep loss beginning at 1000 Hz and reaching the 80 dB level at 4000 Hz.

Both temporal bones displayed bilateral foci which were relatively large, hard, and rather well vascularized (cf. Fig. 1). These foci were considered to be inactive. Their extent was almost

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*Not included in Tables 1 and 2.

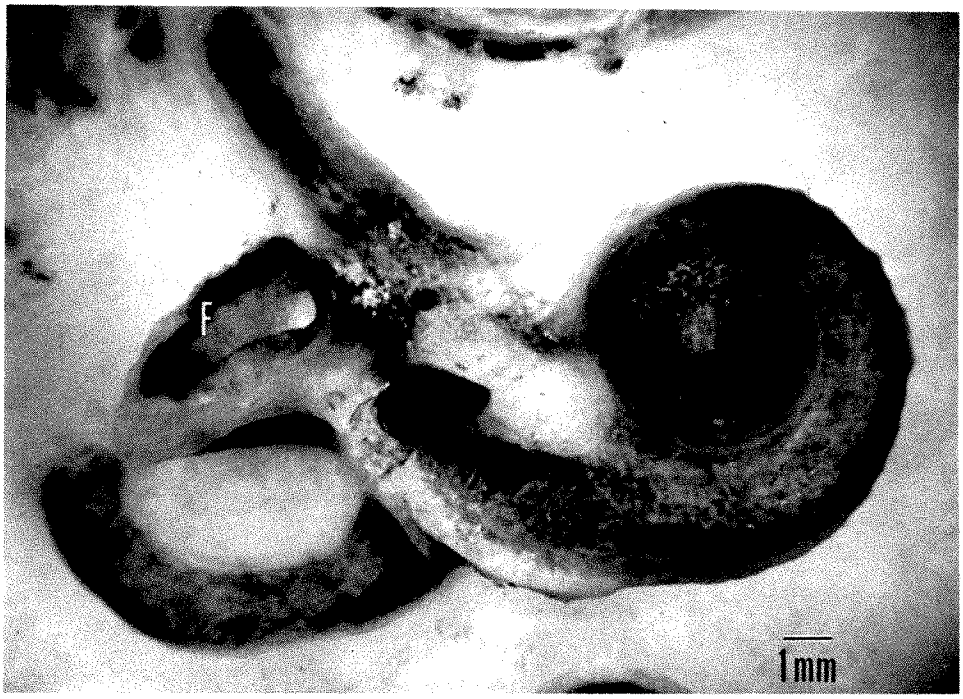

Fig. 11. (Case 5) Right ear. Relatively large, whitish, anterior focus, extending from the oval window to the upper basal turn. The focus was hard and poorly vascularized, and was judged to be inactive. Only a few blood vessels were stained by OsO_4, and they are faintly seen as minute, dark dots. Note the large fenestration (F) in the horizontal canal (cf. Fig. 22).

identical with that in Case 5, pictured in Figure 11. However, they did not extend quite as far anteriorly and they were not close to the spiral ligament in the upper basal turn. There was a relatively severe sensorineural degeneration in the lower half of the basal turn and severe loss of outer hair cells in the middle and apical turns. It could well be argued that this patient displayed more hearing loss and sensorineural degeneration than is generally seen in this age group, and thus his hearing loss could have been caused by otosclerosis.

MULTIPLE FOCI AND DIFFUSE OTOSCLEROSIS

Cases 2, 3, 4 and 7 had two or more foci, most of which were poorly outlined. The most extensive involvement of the otic capsule and the most severe labyrinthine damage were found in this group, which included two pairs of specimens plus two single right ears. All cases showed severe sensorineural degeneration and in five specimens there was also severe involvement of the round window, with occlusion or stenosis. In the remaining specimen there was only a mild narrowing of the window. All but this last one showed new bone formation in the scala tympani.

The most interesting specimens were a pair of temporal bones obtained from a 71-year-old male, Case 3, who had worn a hearing aid for a brief period when he was in his early twenties but had been completely deaf since his 24th year. The history of this patient, obtained from his wife, was rich in a variety of labyrinthine insults. The hearing loss began at the age of 12 when he had diphtheria or scarlet fever. At the age of 19 he had an attack of malaria and high fever, which was treated with quinine. That treatment for all practical purposes took most of what was left of the patient's hearing. He had

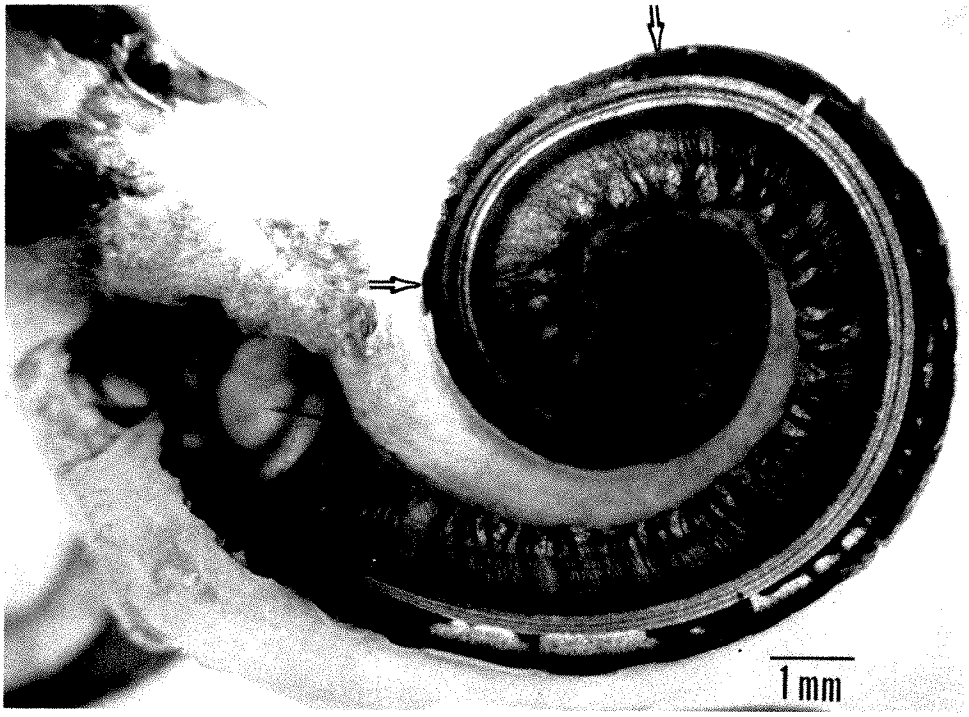

Fig. 12. Same ear as in Fig. 11. The apical turn and half of the middle turn have been removed. Note the circumscribed nerve degeneration (arrow) extending basalward from the focus. There is no precise correspondence between the focus and the inner ear lesion like that in Case 1 (cf. Figs. 2-5).

also worked in noisy surroundings for 25 years, but this exposure was probably not of significance, since it occurred after he had lost his hearing. In his younger years he suffered greatly from "bells ringing" in both ears, to the extent that he greeted the complete deafness at age 24 with relief since it was accompanied by a great reduction in the tinnitus. However, the tinnitus did continue to some extent for the rest of his life. Until his very last days he suffered from attacks of vertigo, which apparently were quite disturbing. During these attacks the tinnitus increased. In addition, he had a feeling of fullness in his ear, but his wife could not remember whether this was in the left ear, which he referred to as his "bad ear," or in the right ear.

Both labyrinths showed extensive, more or less symmetrical capsular otosclerosis, with ankylotic stapes, thickened footplate, and partially occluded oval window. The otosclerotic process was diffuse and the exact extent of the lesion was difficult to evaluate in this pair of bones. A clear line of demarcation was seen only at the horizontal and superior canals. Most of the abnormal bone was firm, but there were three soft, darkly-stained, and active areas visible at the superior canal, at the oval window, and at the apex in both bones. The bony changes in the right ear were unusual, in that there were two large cyst-like cavities in the temporal bone. These cavities, which were empty and were lined with a thin layer of tissue, may, in vivo, have been filled with extracellular fluid. One cavity was located close to the round window, and the second at the apical turn (Fig. 14). The curved outline of the turn was clearly seen on the medial wall of the apical cavity where the spiral ligament was covered with only a thin layer of bone which was brittle and much softer than normal otic capsule.

In both labyrinths there was exten-

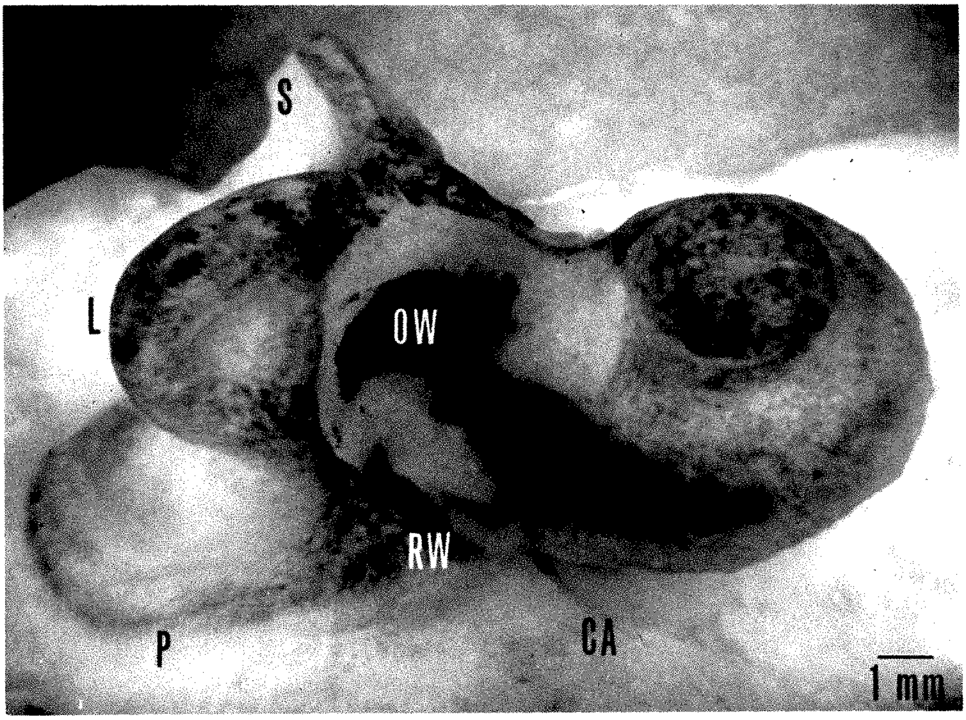

Fig. 13. Large, whitish, poorly vascularized focus surrounding the oval window (OW). It extends in one direction to the round window (RW) and in the other anteriorly to the upper basal turn, as in Fig. 11. No obvious sensorineural degeneration related to the focus (judged to be inactive) was seen in this preparation. S - Superior canal; L - Lateral or horizontal; P - Posterior canal; CA - Cochlear aqueduct.

sive new bone formation expanding into the scala tympani in the lower half of the basal turn. The new bone was solid and fused with the osseous spiral lamina, which was rigid in this area. The round window and opening of the cochlear aqueduct were completely covered by bone and occluded on both sides (Fig. 16). Both temporal bones displayed severe sensorineural degeneration, but the basilar membrane was covered with more than a thin layer of epithelium. A distinct band of supporting elements was still seen on both sides throughout the cochlea. The left cochlea had only two complete turns, a condition which could be interpreted as representing a mild malformation or incomplete development.

On the right side the reticular lamina and the heads of the inner pillar cells were clearly present, but on the left side no pillar heads were visible. The tectorial membrane was atrophic on the left and partly rolled up in the inner sulcus. In all turns the membrane was partly calcified. There was bilateral severe neural degeneration with a very sparse network of lightly-stained nerve fibers visible only in the most apical 1.5 mm of the basilar membrane on the left side. On the right a sparse nerve network was present from the lower middle turn on, in the apical 13 mm of the cochlea (Fig. 16). The network rather abruptly became darker and more dense in the most apical 1.26 mm of the cochlea. Both bones demonstrate the fact that even after long-lasting deafness some nerve fibers usually remain in the apical portion of the cochlea.[64,65]

On each side we found one or two myelinated nerve fibers taking a long and winding spiral course on the basilar membrane in the basal turn. On the left side, they ran for up to 1.3 mm, ending in loops. This is an unusual phe-

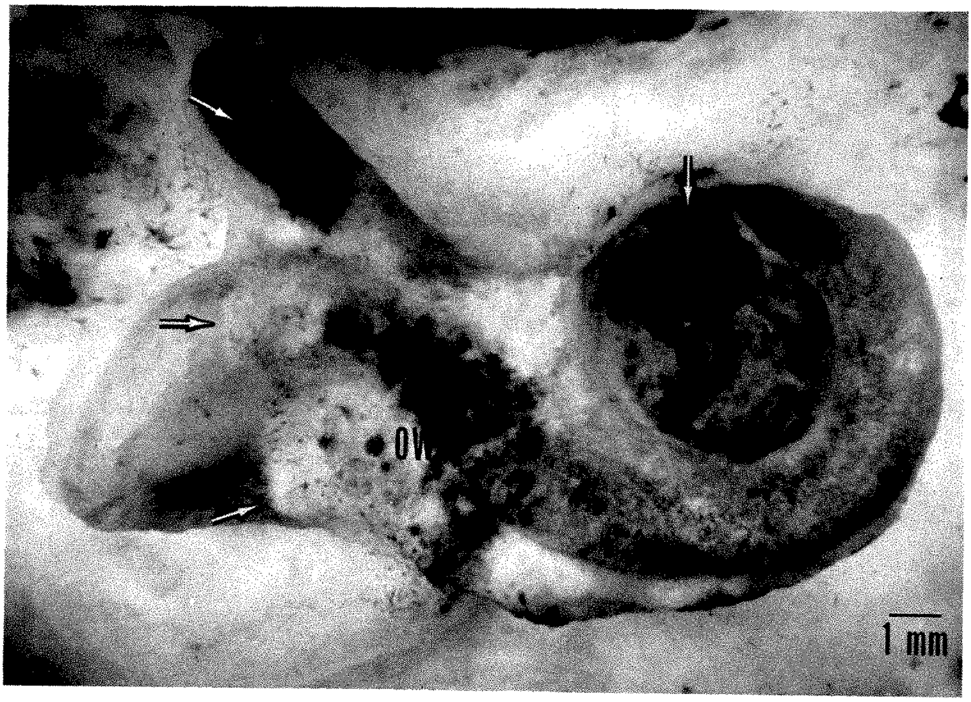

Fig. 14. (Case 3) Right ear from a 71-year-old male, with multiple and diffuse foci. The darker active areas are soft and porous and have been penetrated and stained by the perilymphatic perfusion of OsO_4. The region of the oval window (OW) is completely occluded, with a hole drilled for perfusion. Arrows to the left indicate the posterior border of the otosclerotic process. Note at the apex (vertical arrow) a large cyst-like space in the otic capsule, opened to show the thin, darkly-stained bony covering of the apical turn.

nomenon, which we have occasionally observed in man and experimental animals, always in association with severe sensorineural degeneration.[25] We have never seen fibers like these in normal material. The phenomenon in all likelihood represents a regeneration and bizarre growth of dendrites coming from surviving ganglion cells.

On the right side there was a slight *cochlear hydrops,* but the saccule was ruptured and wide open, with parts of the dilated walls still standing and extending into the vestibule, and other parts collapsed onto the macula. On the left side there was a pronounced cochleosaccular hydrops, the most severe we have seen in our temporal bone collection (Fig. 15). The distension of Reissner's membrane was very uneven, especially in the basal turn, where parts of the membrane reached and were adherent to the bony modiolar wall. Other parts again were partially collapsed. Reissner's membrane herniated through the helicotrema into the scala tympani, where it extended all the way basalward to the lower turn.

In neither ear were the epithelial cells lining the endolymphatic side of the expanded Reissner's membrane larger than usual; in fact they were smaller and more numerous than those normally present, particularly on the left side. This is a common finding in our cases of hydrops labyrinthi, indicating that, rather than becoming stretched, Reissner's membrane grows by cell multiplication in response to an increase in endolymph. We believe that this growth occurs from the margins, particularly at the limbus. On the left side, however, several dense clusters of normal-appearing epithelial cell nuclei were observed scattered on the membrane. These areas could be sites of intensive growth and renewal of epithelial cells in the membrane proper. Further discussions of

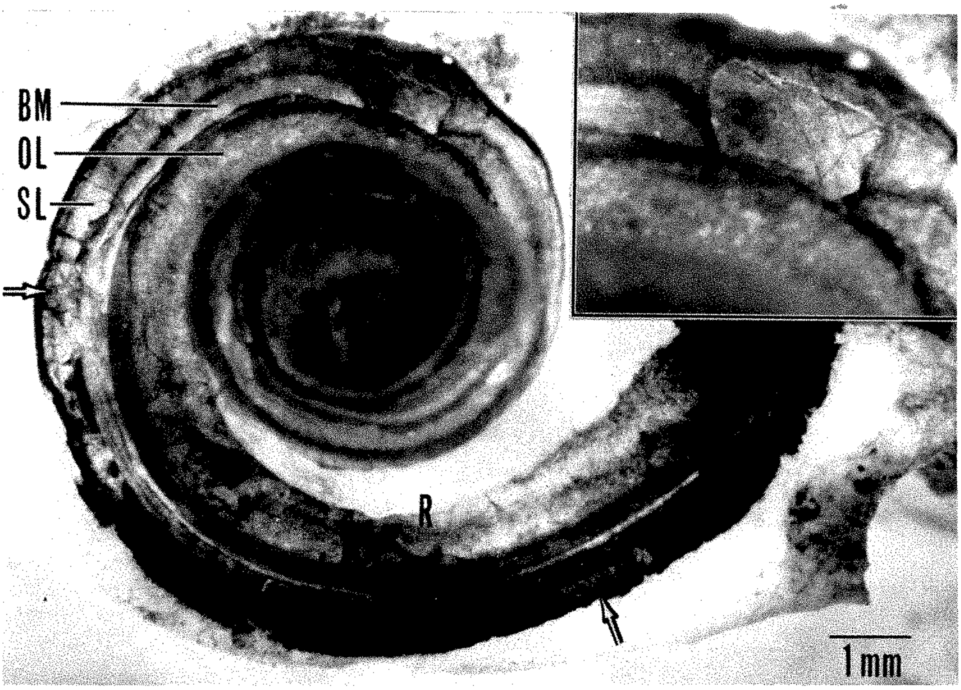

Fig. 15. (Case 3) Left ear showing almost total sensorineural degeneration. BM - Basilar membrane; OL - Osseous spiral lamina; SL - Spiral ligament. Arrows at the bottom and the left show examples of extreme atrophy of the spiral ligament with empty cyst-like spaces. R - Portion of hydropic Reissner's membrane seen attached to the bony wall of the scala vestibuli. Insert: Note in the upper basal turn a large defect in the basilar membrane.

changes in Reissner's membrane in hydrops will be reserved for a separate report.

Both temporal bones showed extensive atrophy of the spiral ligament and stria vascularis. In fact, the spiral ligament on the left showed the most severe atrophy that we have encountered in our collection. This atrophy apparently caused the large empty cyst-like spaces which were found bilaterally throughout the cochlea in the ligament in the lower half of the scala media and in scala tympani.

The left temporal bone showed interesting and, in our experience, unique *basilar membrane pathology*. There was a large defect, extending 1.5 mm on the basilar membrane in the upper half of the basal turn (Fig. 15). The basilar membrane in the middle and apical turn was in an abnormal position because its outer attachment to the spiral ligament was shifted towards scala tympani. Thus the basilar membrane did not lie in the same plane as the osseous spiral lamina, but formed an obtuse angle with it. In the upper half of the middle turn and in the apical turn there were five small, slightly oblong holes, approximately 60 to 80μm in diameter, located just at the former site of Corti's organ or just outside it. All of the holes had their long axis directed more or less radially. The remaining band of supporting elements in these areas was unevenly atrophied, and almost interrupted. There was a large clump of white solid concretions on the basilar membrane in the upper basal turn, not far from the large defect. Through this hole Reissner's membrane had herniated into the scala tympani in a very complicated pattern of foldings and now extended basally to the area of new bone formation.

There were the usual forms of vascular pathology frequently seen in old pa-

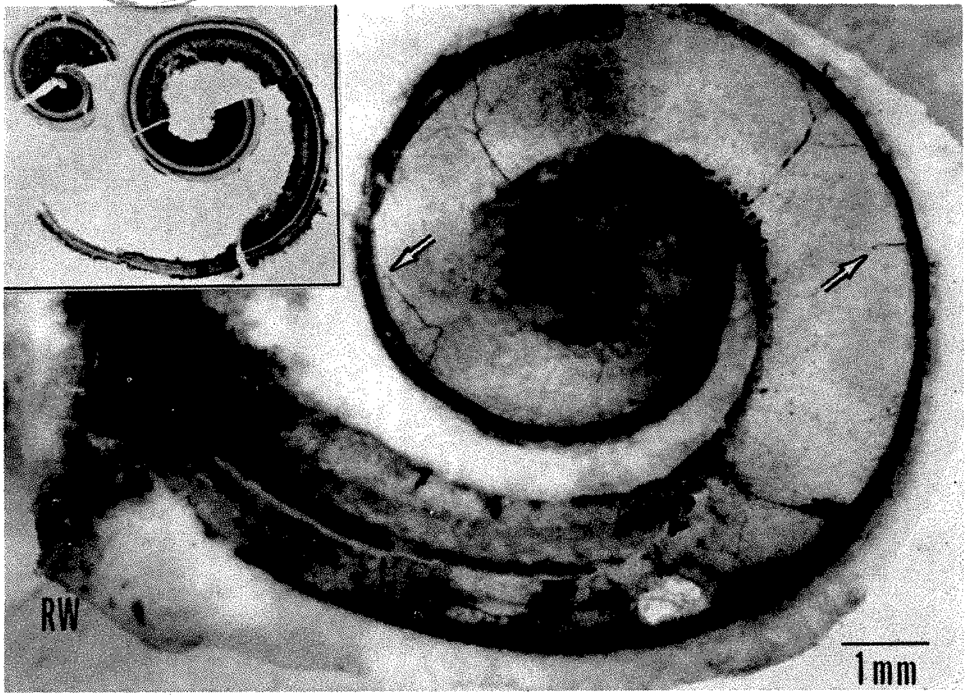

Fig. 16. (Case 3) Right ear (cf. Fig. 14), with the scala tympani exposed, showing the new bone formation adherent to a rigid portion of the osseous spiral lamina. The round window and the cochlear aqueduct are covered by the new bone. The hole in the lower basal turn was drilled as a new outlet for perfusion. Vascular shunts are seen at the arrows. Insert at upper left shows the osseous spiral lamina with numerous nerve fibers remaining in the middle and apical turn, despite long-term deafness.

tients with sensorineural degeneration and presbyacusis. Only the more striking aspects of vascular pathology will be described. In the right temporal bone several of the radiating arterioles were dilated. No outer spiral vessel was visible in the lower basal turn. In the left, no outer spiral vessel was found below the defect in the basilar membrane of the upper basal turn. In the remaining areas there were long stretches of basilar membrane without an outer spiral vessel.

In the scala tympani of the right ear two vascular shunts were observed in the basal turn (Figs. 16, 17). The one in the lower basal turn had a course similar to that described in Case 1. After a radial path the vessel penetrated the bone perpendicularly. In the upper basal turn there was a single candelabra-shaped formation of minute collecting vessels without the usual venule passing radially toward the modiolus. Instead, this particular plexus apparently was drained by a vessel penetrating the bone and leaving the scala just below the basilar membrane. Both of these shunts differed markedly from that seen in Case 1, since they had the diameter and appearance of normal capillaries.

The most extensive and active involvement of the otic capsule was observed in a pair of temporal bones from a 61-year-old man, Case 2 (Fig 18). This patient had been a machinist and toolmaker working in noisy surroundings for more than 30 years, and was said to have been hard of hearing for at least that long. He had not complained of tinnitus or vertigo. An audiogram taken six years prior to his death showed a bilateral hearing loss of 100 dB at 500, 1000, and 2000 Hz and no response at 4000 and 8000 Hz. (His wife had long suspected that the hearing loss was psychosomatic.)

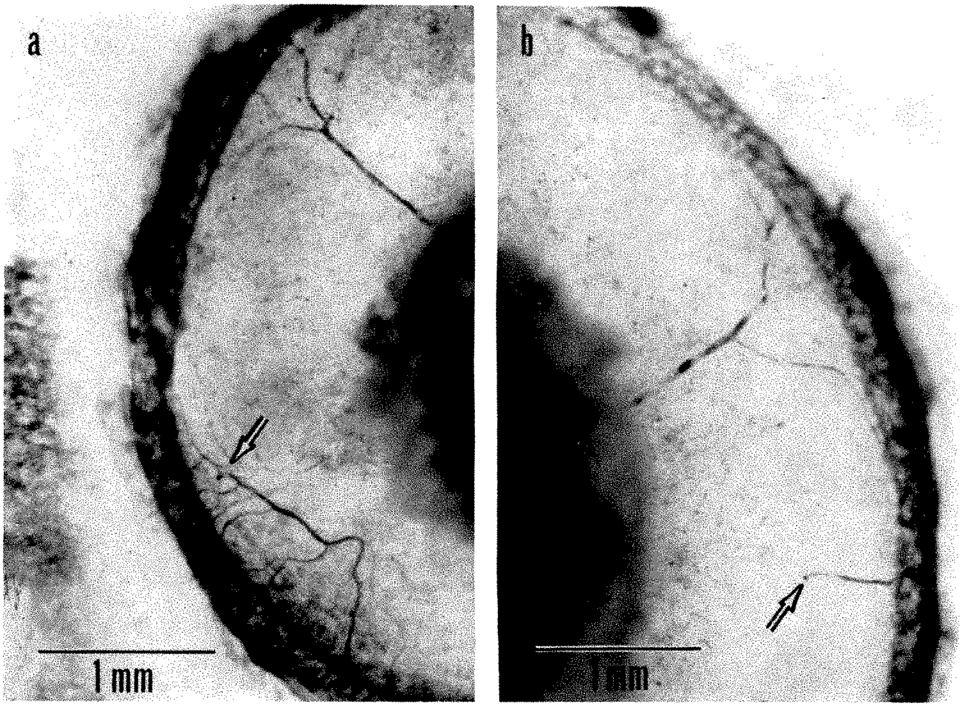

Fig. 17. Close-up of the vascular shunts (arrows) in the scala tympani seen in Fig. 16. In a) minute collecting vessels forming a regular candelabra pattern are presumably draining into a capillary-sized shunt penetrating the bone. In b) a single radial vessel is seen interrupting its course and penetrating the bone instead of draining into the spiral vein as do the vessels above and below it.

The bilateral, active, otosclerotic process which was more or less symmetrical, involved most of the bony labyrinth, excluding only the middle and apical turns of the cochlea, the posterior canal and the posterior and medial aspects of the vestibule. There were multiple soft, highly vascular foci, frequently fused together, along the entire length of the basal turn, involving all three scalae. There was widespread new bone formation extending into the scala tympani throughout the lower half of the basal turn (Fig. 18). These changes were similar to those in the previous case, but more severe. The new bone was solid and fused with the osseous spiral lamina, which was opaque and rigid throughout the lower basal turn, even in areas where there was no direct contact between the lamina and the exostotic bone. As in the previous case the round window was occluded on the left side, but a small aperture was present on the right side. The openings of both cochlear aqueducts were hidden under bone. The scala tympani was very narrow in both bones above the round window region. The endosteum in all three scalae of the basal turn was thickened; that covering the bone extending into the scala tympani was very thick and dense. It was peeled off in thin layers for examination of blood vessels. The growth of lamellar bone in the scala tympani in these two cases was similar to that observed by F. R. Nager and Fraser[66] and by other authors.

Changes in the membranous cochlea were also symmetrical. Conspicuous sensorineural degeneration was present throughout. The nerve degeneration was very severe in the lower half of the basal turn, but only mild in the rest of the cochlea (Fig. 18). In both cochleas there was a complete loss of outer hair cells, but supporting cells and numer-

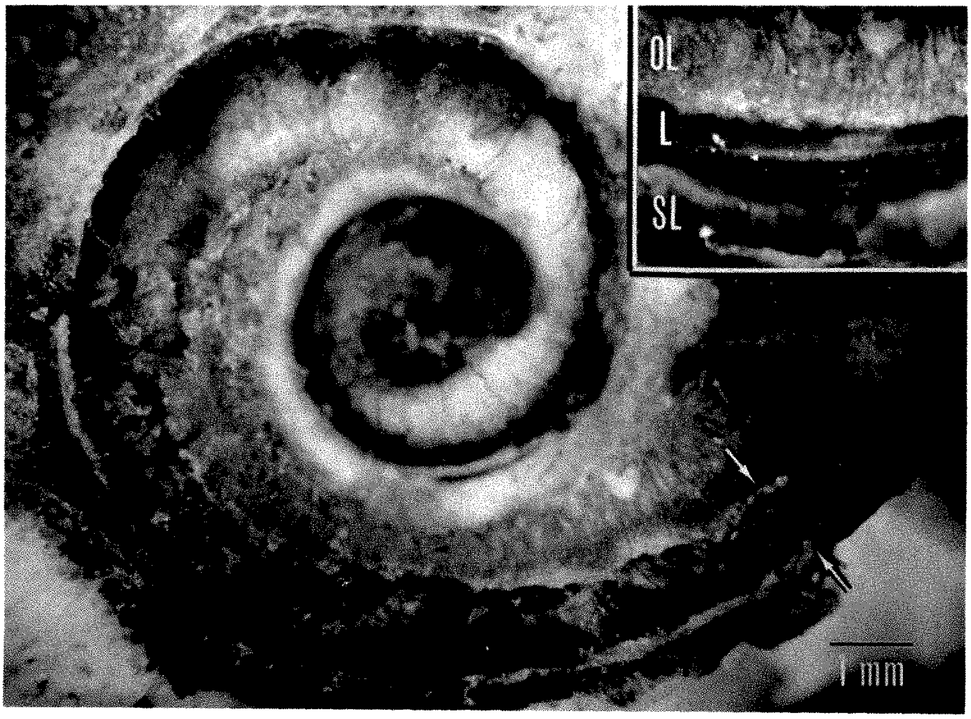

Fig. 18. (Case 2) Scala tympani of left ear, showing the most severe form of capsular otosclerosis seen in this study. There were multiple soft, well-vascularized, and darkly-stained foci in the upper half of the basal turn, which were judged to be active. Note the massive new bone formation extending into the lower half of the basal turn, narrowing scala tympani (arrows) and covering the round window and the cochlear aqueduct (cf. Fig. 19). There was a severe loss of capillaries and venules. Insert: Close-up of the pathological osseous spiral lamina (OL), in the lower half of the basal turn. The lamina was thick, opaque, rigid and fused with the new bone in the scala tympani. Note the very severe nerve degeneration. L - Limbus spiralis; SL - Spiral ligament. The translucent basilar membrane in between appears dark because of the staining of the thickened endosteum of the scala tympani (cf. Fig. 3).

ous inner hair cells remained in all three turns. The patient's history of noise exposure could explain some of the sensory and neural degeneration, but the total loss of outer hair cells was, in all likelihood, caused primarily by the active otosclerotic process.

The vascular changes were not unlike those described in the single bone from Case 1. A few arterioles and several venules were noticeably dilated. There was some strial atrophy, but the strial capillaries were of normal size. The spiral ligament in the basal turn was thickened, dense, and fibrotic. There was a severe loss of capillaries and of a few arterioles as well in the spiral ligament, much more so than one would expect in an ear from a patient of this age. There was also a notable lack of vessels in the scala tympani in the basal turn. In the stenotic part of the scala tympani we could trace only a few vessels coming from the spiral ligament toward the modiolus along or through the newly-formed bone (Fig. 18). Also in the upper basal turn, where there was no expanding process, there was a marked loss of venous capillaries; a few venules were also missing. Examination of the endosteum from the exostotic bone revealed two or three large blood vessels emerging from it and continuing toward the modiolus. These apparent shunts resembled those described by Rüedi and Spoendlin.[10] The outer spiral vessel was present and in part slightly dilated in the basal turn.

Both temporal bones of Case 2 also showed vestibular pathology, which will be described under a separate heading.

The right ear from a 62-year-old man, Case 4, with a profound sensorineural degeneration, showed, as expected, the most severe changes in the basal turn, with only a few thin nerve fibers and some unrecognizable supporting elements remaining. However, in addition there was a stretch of equally severe nerve degeneration in the upper middle turn, apparently related to complete loss of inner hair cells in this region. Basally and apically to this lesion a dense nerve network prevailed and several of the inner hair cells were present. Circumscribed degeneration in the middle turn is unusual and could in this case have been secondary to otosclerosis.

The sixth specimen in this group, i.e., Case 7, the right ear from a 65-year-old man, showed no unusual findings apart from a very severe outer hair cell loss. This was the only bone of the multiple-focus group which did not show new bone formation in the scala tympani. The nerve degeneration was limited to the first quadrant of the basal turn and was possibly related to an active focus in the scala tympani just anterior to the round window and more or less under the area of maximal pathology. Even so, because of the prevalence of sensorineural degeneration in this area in non-otosclerotic ears, a causal relationship could not be established.

OTOSCLEROSIS CONFINED MAINLY TO THE ROUND WINDOW

In one pair of temporal bones the otosclerotic changes were seen for the most part at the round window. These bones were obtained from a 49-year-old man* who died from meningitis. He was a chronic alcoholic with cirrhosis of the liver. The patient had otitis media on the right side, and the meningitis was assumed to be of otogenic origin. A stapedectomy had been performed in the right ear several years before his death, but the patient was deaf in that ear. An ankylotic stapes was found in the left ear. According to his wife he had some hearing remaining in this ear when using a hearing aid.

Both the right middle ear and labyrinth were filled with pus. There was a mobile Teflon® prosthesis in the oval window. The clinical diagnosis was thus supported by the dissection findings, and the route of infection to the meninges most likely went through the inner ear. There was no infection in the left ear. The stapes was completely rigid and the footplate was thick.

The right round window was almost completely occluded by hard bone, and only a very narrow aperture remained. There was also a small focus anterior to the oval window. The left round window was completely closed by solid bone. A careful drilling of the bone in the niche revealed what we believe was a complete occlusion. A vessel of capillary size was seen running from the pathological bone radially to the spiral ligament (Fig. 19).

The right cochlea showed widespread outer hair cell loss with several fresh scars, indicating that the degeneration was recent and presumably a result of the otitis interna. No obvious specific pathology was observed in the left ear, with the exception of the single vascular shunt already mentioned. There was sensory and neural degeneration mainly in the lower quarter of the basal turn, perhaps slightly more advanced than one would expect in a 49-year-old man.

VESTIBULAR PATHOLOGY

Only one pair of temporal bones, Case 2, and a single bone, Case 4, showed vestibular pathology that was obviously related to capsular otosclerosis. We found no specific pathology in Case 1, although the focus did extend to the vestibular system (Fig. 2).

As mentioned above, the otosclerotic process in both bones of Case 2 involved large areas of the horizontal and superior bony ampullae and canals. The right horizontal canal was partly occluded by otosclerotic bone. The process

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*This case not included in Tables 1 and 2.

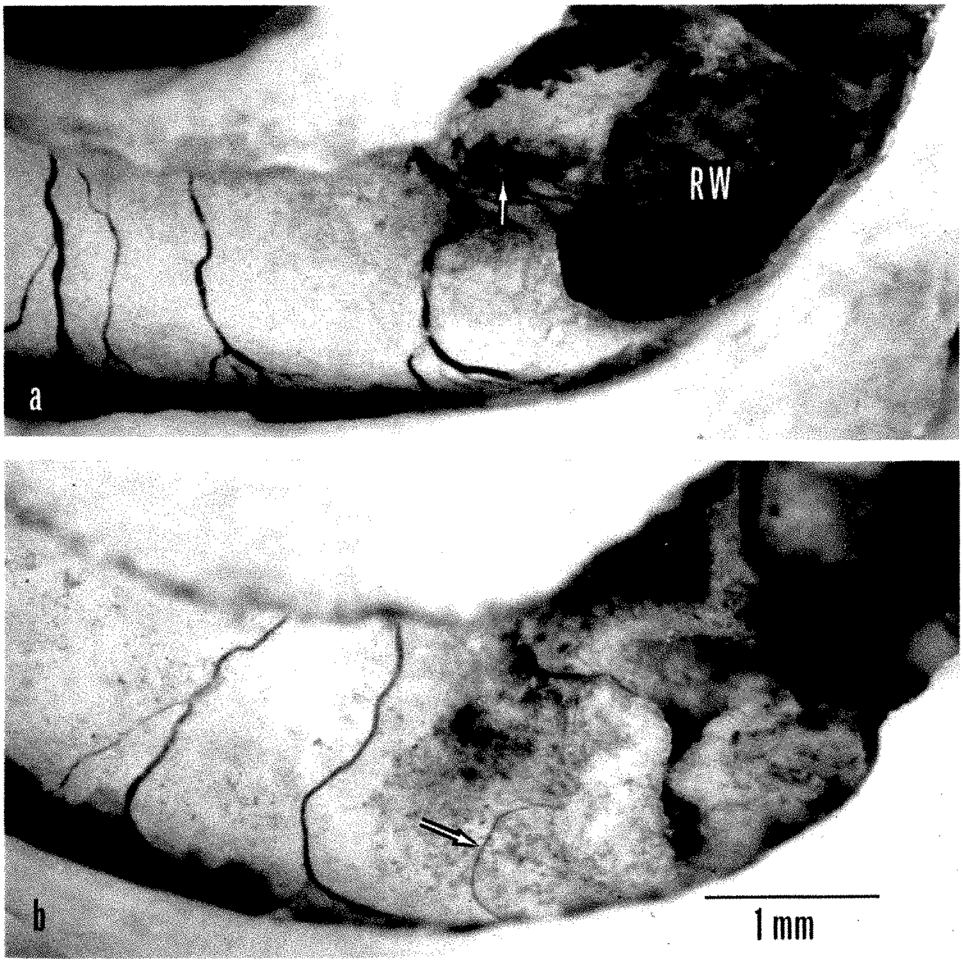

Fig. 19. Close-up of scala tympani adjacent to the round window in a) the normal cochlea from a teen-ager; b) the left cochlea from a case with round window otosclerosis. RW - Normal-appearing, darkly-stained round window membrane. The vertical arrow points to the funnel-shaped opening of the cochlear aqueduct. Four venules are seen to the left. Note in b) the entire round window completely occluded by the otosclerotic bone. The slit seen ends blindly. The oblique arrow points to a vascular shunt connecting the otosclerotic bone with the vessels of the spiral ligament (cf. Figs. 10, 16 and 17). The process was sclerotic and was judged to be inactive.

involving the vestibular portion was judged to be active on the right side, but more or less inactive on the left.

On the right side all three membranous ampullae were partly collapsed. The horizontal membranous canal was almost occluded at the site of atresia. A portion of the membranous wall of the utricle was also collapsed and adherent to the center of the macula. All three cristae and both maculae showed complete loss of hair cells. No superstructures were seen. The cupulae could have been lost in the process of dissection, but the otoconia and the otolithic membranes, which are always readily visible, had obviously been missing in vivo. The planum semilunatum was completely absent in the superior and horizontal membranous ampullae. Large, thin walled vesicles were seen at the site of the planum (Fig. 20) and around the utricular openings of these ampullae.

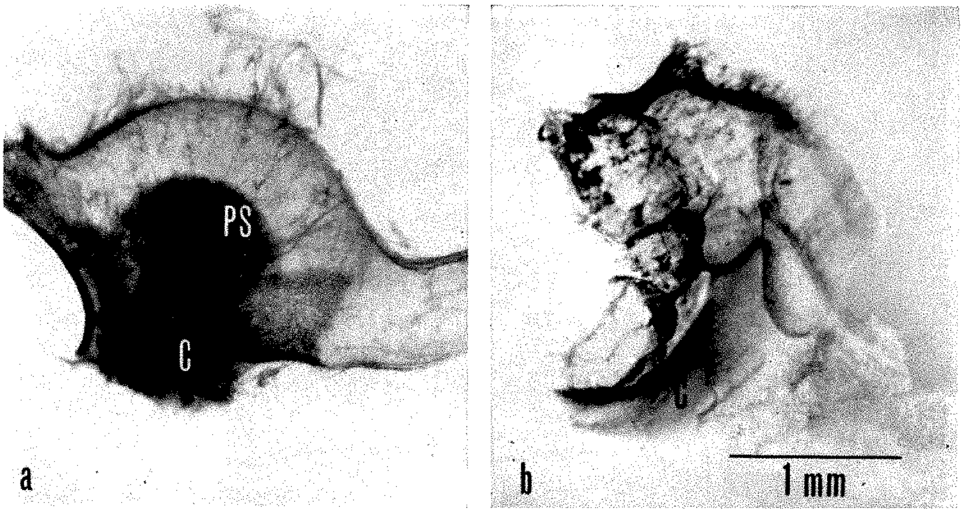

Fig. 20. a) Normal-appearing membranous horizontal ampulla cut in half longitudinally. b) Similar preparation from the right ear, Case 2, which had extensive involvement of the vestibular bony labyrinth. C - Crista; PS - Planum semilunatum. In a) there is a well-defined pigmented area to the right of the crista. In b), note the complete absence of planum semilunatum. There are several large vesicles at the site of the planum and around the opening into the utricle.

In the pigmented areas of the membranous wall of the normal utricle there are several scattered populations of light and dark polygonal cells. In light microscopy these areas show certain similarities to the planum semilunatum, which also often displays a double population of light and dark cells. These cells in the wall of the utricle presumably correspond to the so-called "dark cells" described in the utricular wall of the guinea pig by Nakai and Hilding;[67] Kimura;[68] and others. The "dark cells" resemble strial marginal cells and presumably participate in the regulation of the vestibular endolymph. It is interesting to note that in the right ear these dark cells were entirely absent.

The vestibular changes in the left ear were similar, but somewhat less pronounced. There was no collapse of the membranous labyrinth, and a regularly shaped planum was seen in the ampullae. Superstructures were present, but no otoconia were seen. Most of the sensory cells were degenerated.

An ENG recording was available for only one patient, viz, Case 4, which was represented by the right ear, with extensive and diffuse otosclerosis, and multiple foci. The vestibular organs were examined by scanning electron microscopy. In all three cristae sensory cells were completely absent. This finding was in good agreement with the ENG, which showed a complete lack of caloric response. It is worth noting, however, that the maculae of the utricule and saccule had many hair cells present, although severly reduced in numbers (Fig. 21).

Case 3, the 71-year-old male who had severe hydrops on the left and extensive otosclerosis involving the vestibular system as well, showed no unusual sensorineural degeneration of vestibular endorgans with the exception of the right saccule, which was ruptured and had severe loss of sensory cells from the macula. The ampullar cristae and utricular macula showed some diffuse and patchy loss of sensory cells, but because of the age of the patient this finding was not considered significant.

Abnormal saccular otoconia were observed in Case 3 forming a rigid crust, which consisted of spherules of apatite rather than the normal flexible layer made up of individual crystals of calcite. Virtually identical crystals of apa-

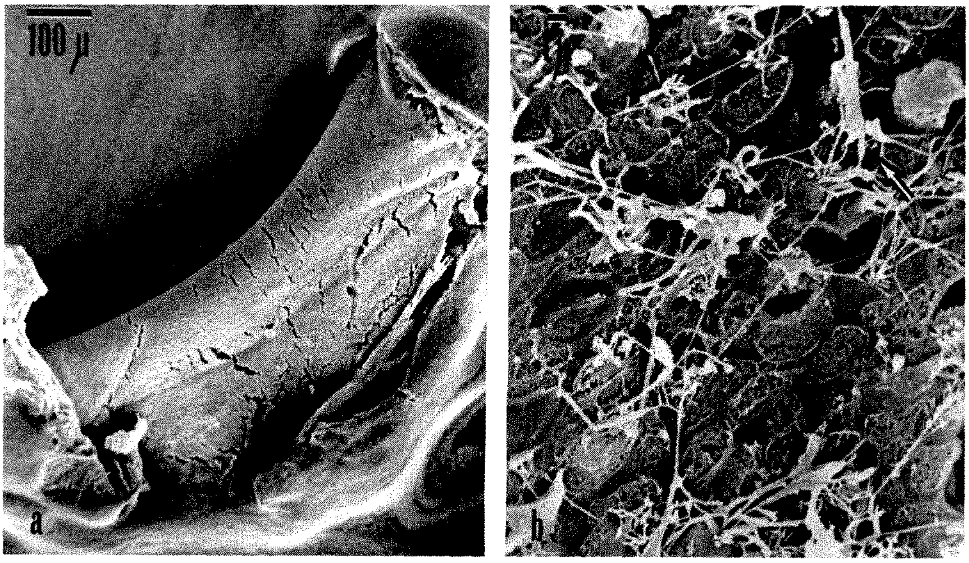

Fig. 21. (Case 4) Scanning electron micrograph showing a) the horizontal crista with complete absence of sensory cells and their cilia; b) a higher-power view of the macula sacculi with several tufts of cilia present, though probably affected by autolysis. There was no response to caloric stimulation, but this was hardly a "dead labyrinth."

tite were found in the partially collapsed saccule from a case with a small anterior focus. In this and in another case as well, abnormal calcite crystals were observed on the utricular macula.

We have made similar observations in material from nonotosclerotics. It is therefore too early to postulate a causal relationship between otosclerosis and abnormal otoconia. These and related findings will be described in detail elsewhere.

Vestibular pathology was seen in four fenestrated ears. Cases 5, 6, 7 plus another bone representing clinical otosclerosis but with no visible focus, were obtained from patients who had undergone fenestration operations before the time of stapes mobilization and stapedectomy. In Case 5 the fenestration had been performed 31 years before the patient died at the age of 74. An unusually large fenestra nova was found in the horizontal canal, extending into the bony ampulla (Fig. 11). The fenestra was covered by a thick, flexible layer of tissue. Beneath the fenestration, the membranous duct was completely absent and the perilymphatic space was sealed off from the vestibule and from the distal portion of the bony canal by two thin membranous walls. A third thin partition was found nearer the nonampullated end of the canal, enclosing a stretch of the duct, which was collapsed (Fig. 22).

All three membranous ampullae were also collapsed. Their openings to the utricle appeared more or less closed. The membranous wall of the utricle was collapsed and adherent to the anterior half of the macula. No otoconia were seen but there were some remnants of the otolithic membrane on the posterior half of the macula.

All three cristae showed very severe hair cell degeneration under the scanning electron microscope. The macula utriculi had no hair cells remaining, whereas the saccule showed only moderate hair cell loss. There were no otoconia remaining on the saccule, but the otolithic membrane was present. There was a mild neural degeneration in both maculae, which was more pronounced in the saccule. The changes in the saccule, including the loss of otoconia, could probably be attributed to the age of the patient.

All the other specimens had smaller

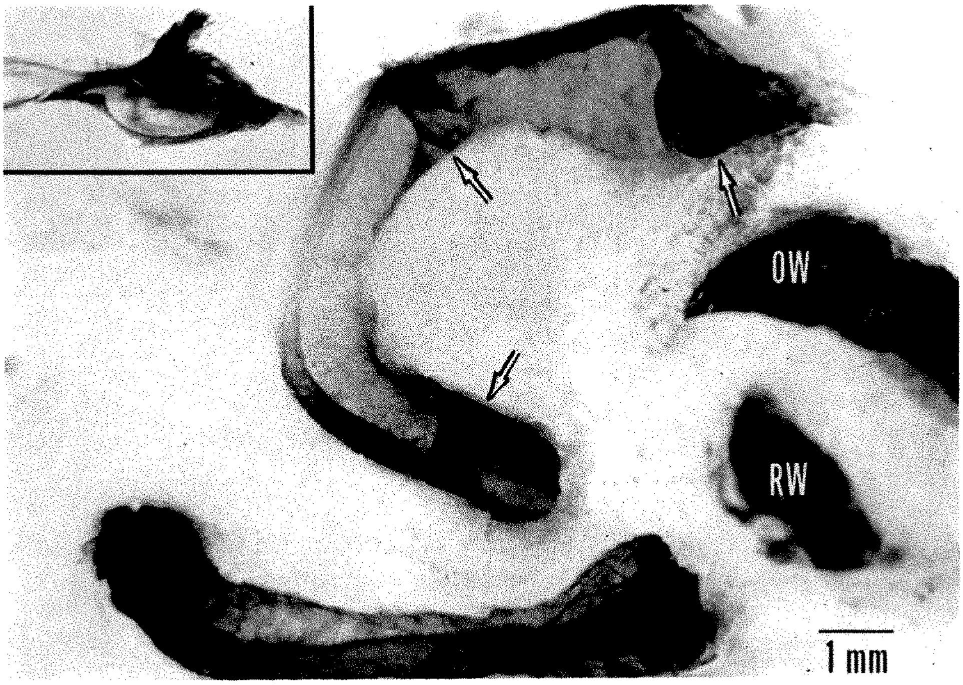

Fig. 22. The horizontal and posterior membranous canals from the same preparations as in Fig. 11, with the otic capsule partly removed. The patient had undergone a fenestration. The membranous canal is missing at the site of the *fenestra nova* (between arrows). At each arrow there was a thin, membranous partition formed in the perilymphatic space. All three ampullae and the utricle were collapsed and showed severe degeneration. Insert: Posterior ampulla, collapsed and having no opening, either toward the utricle or toward the canal.

fenestrations of usual size. In Case 7, there was scarring and ossification with complete atresia of the bony canal just distal to the fenestration. No trace of the membranous canal was seen in the atritic region. All cristae showed a severe but more or less equal degree of hair cell loss. The utricle also showed a similar degree of degeneration, whereas the changes in the saccule were less pronounced.

In the fourth specimen,* the membranous duct was flattened but present at the fenestra, and only two thin partitions were found, one at the ampulla and a second at the nonampullated end of the canal. There was a degeneration of sensory cells in all three ampullae and in the macula utriculi, but these changes were much less severe than in the two previous specimens. The saccule also showed hair cell degeneration, but again milder than in the utricle.

The right temporal bone from Case 6 displayed no pathology which could be related to the fenestration performed 20 years prior to death. There was no new wall formation in the bony canal at the site of the fenestration. Where the membranous duct was still present the ampullar cristae from the right and the left horizontal ducts were carefully compared under the scanning electron microscope. Both cristae showed approximately the same degree of hair cell loss. Similarly, all three cristae from the right ear showed more or less equal amounts of hair cell loss.

An unusual form of pathology, *a fistula of the saccular duct,* was found in the left temporal bone from a 76-year-old woman* who had undergone a routine stapedectomy. There was a round

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*These cases not included in Tables 1 and 2.

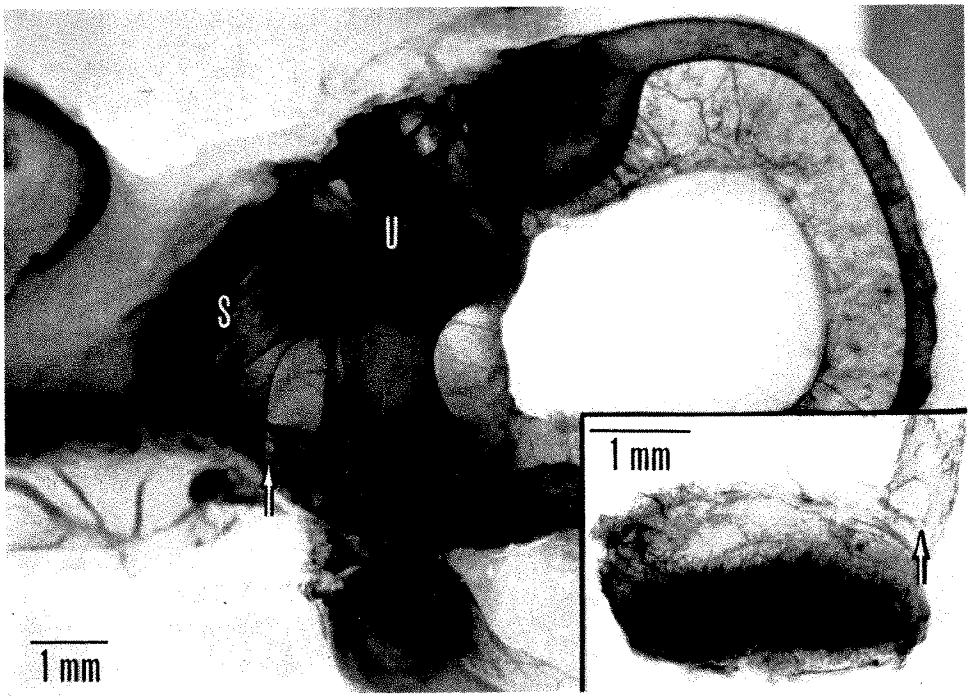

Fig. 23. Dissection showing the vestibular system of the left ear. S - Saccule; U - Utricle. Note the relatively large fistula in the saccular duct (arrow). Horizontal membranous ampulla and canal at the right. The posterior ampulla is seen at the lower margin. Insert: Close-up of macula sacculi and saccular duct. The neuroepithelium has been dissected off. The fistula in the duct is clearly seen (arrow).

opening in the wall of the saccular duct facing the vestibule. The fistula, approximately 0.4 mm in diameter, was large considering the size of the duct, and was located close to the saccule (Fig. 23). The duct was split in half and was made into surface preparations. Under higher power phase-contrast microscopy we could observe that the fistula was roundish with smooth, thickened margins, which were lined with elongated epithelial cells. The fistula was therefore not a dissection artifact, but must have been formed in vivo, and may possibly have been present from birth.

The saccule showed moderate hair cell loss, and there was sensorineural degeneration in the basal turn of the cochlea. These changes were all within normal limits, considering the age of the patient.

DISCUSSION

The number of temporal bones in this study is relatively small, and no general conclusions should be drawn from it. Even so, it is sufficient to reflect some general tendencies of this enigmatic disease.

No cases of cochlear or histological otosclerosis were found. The latter form was not uncommon in Guild's material[1] and as implied earlier, the absence of histological otosclerosis in our study could perhaps, at least in part, be blamed on the dissection technique which may not reveal all small foci. The small anterior focus, the most common form of otosclerosis, did not cause any obvious labyrinthine changes in our material; admittedly these foci were all judged to be relatively inactive. It is conceivable that prolonged activity of a small anterior focus could cause hair loss in the lower basal turn, but such a possibility is difficult to prove, since varying degrees of hair cell loss are found in this area in virtually all human material. To establish the point would require extensive quantitive evaluation of hair cell populations in otosclerotic and nonotosclerotic ears.

What we have designated as the *large anterior focus* can undoubtedly cause sensorineural degeneration, at least in some cases. Only one temporal bone with an inactive focus extending from both windows to the upper basal turn (Fig. 13) did not show any specific changes, but the rest of the material in this group did show obvious cochlear pathology (Tables 1, 2). Nevertheless, these large foci are relatively small in comparison with the usually massive otosclerotic involvement with which sensorineural degeneration has previously been linked.[4-10] If the causal relationship in some of these cases is still somewhat uncertain, Case 1 is all the more convincing and revealing.

In this temporal bone there was an almost exact local correlation between the circumscribed sensorineural degeneration in the upper basal turn and the active otosclerotic process impinging upon all three scalae (Figs. 4, 5). This finding strongly suggests that the active otosclerotic process may give rise to a substance or substances toxic to Corti's organ. Such substances may diffuse by way of spiral ligament and basilar membrane to injure the neuroepithelium directly, rather than indirectly by altering the function of other cochlear tissues. Had the focus affected Corti's organ by way of the stria vascularis or by altering the inner ear fluids, the changes could hardly have been so precisely localized. Furthermore, we did not see any obvious circumscribed changes in the spiral ligament and stria vascularis. The focus could, in addition, have had a more generalized effect on the hair cells on both sides of the lesion, but examination of Figures 4 and 5 suggests that this was not the case.

This same active focus, extending also to the middle and apical turns and reaching the scala vestibuli and scala media but not the scala tympani, did not cause degeneration in those turns. The sensorineural changes in the lower half of the basal turn could conceivably have been caused by portions of the focus anterior to the oval window (Fig. 3), but for the most part they were probably due to the age of the patient.

One cannot be at all certain whether the active otosclerotic focus acts on the hair cells, the unmyelinated nerve fibers and nerve endings in Corti's organ, the myelinated nerve fibers in the osseous spiral lamina, or on all of these structures. If the facial nerve can serve as a model, it can be postulated that at least the myelinated portion of the nerve fibers is not the primary target. Otosclerotic processes frequently involve the wall of the facial canal, and still these patients do not display any motor weakness of the facial muscles.[69]

Although multiple foci are relatively rare, all specimens, with the exception of one bone in this group, displayed extensive and severe sensorineural degeneration. This finding is in good agreement with other reports of similar cases.[8] Incidentally, it was probably from this form of otosclerosis that Beethoven's deafness arose.[70,71]

Since Case 3 had a history of other labyrinthine insults in his youth as well as otosclerosis, it remains unclear to what extent the capsular otosclerosis was responsible for the sensorineural degeneration found postmortem. Incidentally, this patient, in spite of long-term profound deafness and severe to complete sensorineural degeneration, still suffered from bilateral tinnitus. Conceivably it was of central origin, since it is known that tinnitus can persist even after the cochlear nerve has been sectioned.[72,73]

The right temporal bone from this patient was interesting in that it displayed two relatively large, roundish, empty cysts in the otosclerotic bone. (These cysts were definitely not merely large perivascular spaces.) This finding is most unusual. Lindsay* and Schuknecht** have not encountered similar cysts in their large materials. A review of the literature reveals in fact only one case which is similar to ours. The case was described by Mayer in 1911,[39] on the basis of histological sections. The patient was a 57-year-old male, also with stapes ankylosis, multiple foci, and severe sensorineural degeneration. In addition there was a partially collapsed Reissner's membrane. The right ear showed one such cyst and the left three within the otosclerotic bone. Two of these cysts in the latter specimen appear to be almost identical to those in the present case. We do not know the reason for such formations. Perhaps there was a burst of localized osteoclastic activity in the otosclerotic bone unaccompanied by new bone formation. Our temporal bone was not sectioned, and the fine structure of the bone is not known. It is conceivable, although we feel it is unlikely, that the cysts were caused by a disease other than otosclerosis.

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*Lindsay JR: Personal communication.

**Schuknecht HF: Personal communication.

In all bones with multiple foci the capsular changes were so widespread and severe that the local effect of otosclerosis on the different turns of the cochlea was not obvious. The sensorineural degeneration was most severe in the basal turn, where there was extensive involvement of the scala tympani by otosclerosis and new bone formation (Figs. 16, 18). However, there was hair cell loss throughout, possibly caused by changes in the cochlear fluids as suggested by Chevance and Causse et al.[29-31]

Stenosis of the round window and new bone formation in the scala tympani in patients with multiple foci represents a new type of surgical obstacle. If a cochlear implant should be planned for those usually profoundly deaf patients, considerable bone would have to be removed before any prosthesis could be inserted into the scala tympani. In severe cases it might not be possible to insert an implant at all (cf. Fig. 18).

Is involvement of the scala tympani a prerequisite for degeneration? Why did not the same active focus in Case 1, which caused circumscribed degeneration in the upper basal turn (Figs. 3-5) affect the middle and apical turns — was it because of the lack of involvement of scala tympani in those areas? Examination of more cases is needed to answer those questions. Tracer studies[74-76] have suggested that particles may pass from the scala tympani through the basilar membrane into the intercellular spaces of the organ of Corti and the subtectorial space. Similarly, the transport of hypothetical toxic substances from an otosclerotic focus might occur by way of the perilymph and the basilar membrane.

The finding of a circumscribed sensorineural degeneration adjacent to the inactive focus pictured in Figures 11 and 12 is difficult to explain. The otosclerotic process extended close to the scala vestibuli and scala media, but did not approach the scala tympani. The area of degeneration lies close to the focus, but does not coincide with it as in Case 1. The two could be unrelated, but such circumscribed degeneration so high in the basal turn is most unusual.

Otosclerosis always starts with an active phase, in which normal capsular bone is destroyed. It is likely that all foci have the potential of being "ototoxic" so long as they are active. The degree of possible sensory and neural degeneration most probably depends on the extent and depth of the focus and on the intensity and duration of its active phase. On the basis of our findings in cases with only a small anterior focus, it appears that otosclerotic activity may often be self-limiting. If it is continued, the process may spread to produce a large anterior focus, as in Cases 1, 5, and 6. If it does not spread it may simply burn itself out. Chevance and Causse et al[29-31] have suggested on the basis of ultrastructural and cytochemical studies that lysosomes play an active role in the initial lytic phase of the disease, providing numerous hydrolytic enzymes which take part in bone resorption. It is conceivable that such enzymes could directly affect the organ of Corti during the active stage and cause sensorineural degeneration (Figs. 4, 5).

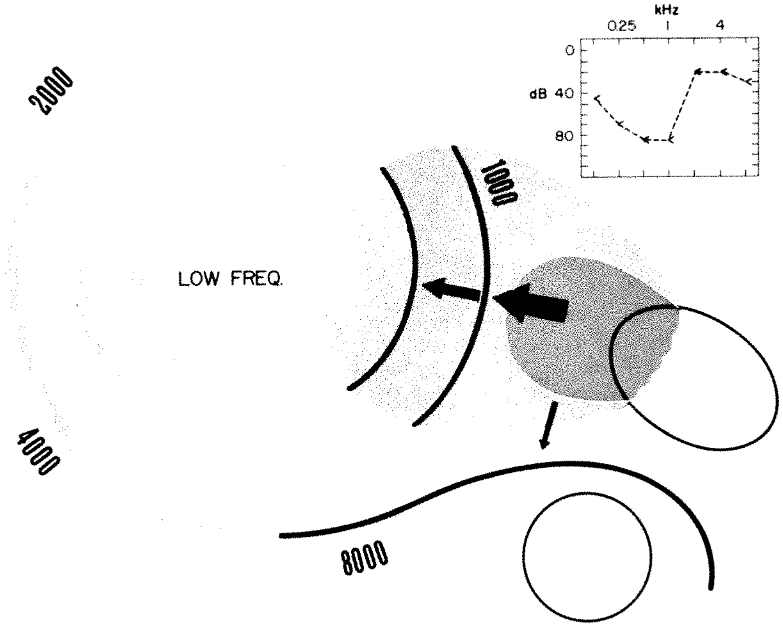

Fig. 24. The shaded area shows the characteristic pattern of expansion of an anterior focus. It is postulated that the upper basal turn represents a site of predilection for sensorineural degeneration caused by a toxic factor diffusing from the active focus (large arrow). Further spread might be expected to affect the middle and apical turns (medium sized arrow) and perhaps the lower basal turn (small arrow). The presence of a specific audiometric pattern in such cases, with a low-frequency "dip" in the bone conduction curve (upper right) is suggested.

The uppermost portion of the basal turn could easily be a site of predilection for circumscribed degeneration. Anterior foci are very common, and a natural direction for them to expand is toward the upper basal turn (Figs. 1, 2, 11, 13). The portion of the cochlear spiral involved corresponds more or less to 1000 and 500 Hz, if one is permitted to make a reasonable extrapolation of the tonotopical map of Crowe et al.[77] One could therefore postulate an audiogram with a low-frequency "dip" as shown in Figure 24. Our two cases did not show any sharp "dips" in their audiograms (Fig. 7), taken 1-2 years before death, at those frequencies. In the first case the hearing loss was so profound that any such dip must have been obscured. Case 5 had a small (15-20 dB) notch in the audiogram at 1000 Hz, but its significance is questionable. The lesions may also have been too narrow to show up clearly in routine clinical audiometry. Furthermore, both ears showed widespread hair cell loss on both sides of the lesion. Carhart[78] has described such low-frequency "dips" in the bone-conduction curves of otosclerotics who also showed an air-bone gap. Similar curves have been shown by Shambaugh.[2,12] It is tempting to assume that many of these patients had otosclerotic foci and sensorineural degeneration similar to that shown in Figures 2-6. (These low-tone dips should not be confused with the well-known "Carhart notch," often seen at 500-2000 Hz in the bone conduction audiograms of otosclerotics. The latter is attributed to the effect of stapes fixation on inertial bone conduction.)

In addition, Carhart[79] has presented a large series of cases, claimed to represent otosclerosis, with mid-frequency dips or "notched losses," but without any conductive component. In the absence of any surgical or histopathological follow-up or air-bone gap in the audiograms it seems unlikely that all of these losses are, in fact, the result of otosclerosis. The possibility that some of them could well have represented a hereditary sensorineural hearing loss does not appear to have been ruled out.

One of the very first cases of otosclerosis to appear in the world literature was reported by Siebenmann in 1899.[27] It showed an almost identical involvement by otosclerosis with that in our Case 1. More recently Sando et al[80] have described a pair of temporal bones prepared by the celloidin technique that are strikingly similar to the case presented here. The bone conduction curve for the right ear is more or less the same as that postulated in Figure 24. Dietzel[81] recently reported a similar case. In the light of these cases, as well as our own, and knowing the common occurrence and the characteristic pattern of expansion of anterior foci, we believe that the degeneration pattern we have described is far more common than an examination of the current literature would suggest.

Three of the temporal bones with active otosclerosis showed forms of vascular pathology which we have not observed in the rest of our material. In these specimens the presence of large vascular shunts between otosclerotic bone and cochlear blood vessels in scala tympani could be confirmed (Fig. 10). Shunts corresponding in size to normal cochlear vessels were found in two other bones which showed no other vascular pathology. There seems to be some hesitancy in accepting Rüedi and Spoendlin's[10] concept of vascular shunts as the major cause for sensorineural degeneration in cochlear otosclerosis. Schuknecht and Gross,[36] Lindsay,[7,8] and others[80] do not even mention such shunts. Altmann,[4] G. T. Nager,[3] and Holleman and Harrill[5] report the presence of vascular connections but attribute little or no significance to them. Kornfeld[82] found greatly dilated strial capillaries in Paget's disease involving the otic capsule, but there were no shunts in his material.

We feel strongly that in no instance could the entire complex etiology of sensorineural degeneration in otosclerosis be explained solely by a "shunt theory." One can only speculate about the importance, if any, of the shunts and the direction of blood flow in them. Would a flow from the focus to the cochlea necessarily have to be so damaging to the microvasculature? It is possible that the huge caliber of the shunt in Case 1 indeed could be indicative of an intense and reversed flow towards the cochlea. The vasodilatation observed in this bone and in the pair of bones from Case 2 could then be indicative of an overloading of the cochlear microcirculation, with venous congestion and anoxia as a result. The vascular pathology could, however, also have been caused by toxic substances from the focus, circulating in the vessels or acting upon them from outside. There is little reason to believe that the vessels of normal appearance forming the shunts shown in Figures 17 and 19 could play an important role in the causation of cochlear pathology, and it is unlikely that the flow in them was directed "upstream" toward the spiral ligament. Some arterioles in the right ear from Case 3 were also dilated, but it is well to remember that we have observed similar vasodilatation in the spiral ligament from elderly patients[24,25] without any otosclerosis.

Judging from our observations, there is no doubt that when active otosclerosis does reach the endosteum of the scala tympani the process can destroy the venous drainage in that area. Loss of venules and venous capillaries in the scala tympani, especially when it is as severe as in Figure 18, must interfere with the cochlear microcirculation and may play an important role in the etiology of sensorineural degeneration. Rüedi and Spoendlin,[10] on the other hand, have proposed that venous congestion actually causes new bone formation in scala tympani, like that in Figure 18. We are more inclined to agree with F. R. Nager and Fraser,[66] who suggested that the otosclerotic process produces irritation of the endosteal layer and thus leads to the formation of new bone in the scala tympani (Figs. 16, 18).

Since there is a relatively well-organized radial arrangement of venules, it is conceivable that a limited loss of venous drainage could also cause circumscribed sensorineural degeneration. We find it difficult to believe, however, that this hypothesis could explain such precise local correlation between bone pathology and sensorineural degeneration as that seen in Figures 4 and 5.

Widespread loss of blood vessels, mainly capillaries, was also observed in the spiral ligament of the scala vestibuli and scala media in Case 2. Active otosclerosis involved the ligament, which was markedly fibrotic. The devascularization was less severe than that in the scala tympani. It appears that the vessels of the scala vestibuli and scala media, which run in the spiral ligament and stria, are better protected against the active otosclerotic process than the vessels in the scala tympani, which lie directly against the bony wall. Vascular changes, including occlusion of capillaries secondary to otosclerosis, have also been described in the middle ear mucosa.[83]

We believe that the left round window in Figure 19 was, indeed, totally occluded by bone, although it is often argued that the closure of the round window in such cases is not complete. Fleischer[84] reviewed serial sections from 99 temporal bones with round window otosclerosis and found that the closure was never complete, although there might be a narrowing down to 50 to 100μm. The question of complete closure or not is mainly academic. The volume of the inner ear fluids displaced in hearing is exceedingly small, approximately equal to that of a single erythrocyte.[85] Movement of such a small amount of fluid might occur somewhere in the scala tympani at "auxiliary pressure outlets,"[86] e.g., along the cochlear aqueduct, at blood vessels which can be compressed, or along empty channels remaining after degeneration of nerve fibers. Thus patients with round window occlusion may hear reasonably well, the hearing loss being no more than approximately 20 dB.[85] Even so, the reliability of the statement that the patient with the left round window completely occluded had some remaining hearing in that ear is questionable, because that ear also had an ankylosed stapes. It should be remembered, however, that fluid displacement in such a cochlea can still occur by means of compressional bone conduction.[85,86]

The ruptures or defects in the basilar membrane and the abnormal position of it in Case 3 (Fig. 15) constitute a phenomenon that we have not encountered in any other temporal bone in our collection. The reason for this finding remains obscure. It is unlikely that it was caused by the hydrops, since Reissner's membrane provided a better route for endolymphatic expansion than the thicker basilar membrane. Neither was there any visible distortion of the modiolus[9] or other bony components of the labyrinth. Schuknecht and Gross and others[34-37] have described similar ruptures and attribute them to atrophy of the spiral ligament. It is interesting to note that the atrophy of the spiral ligament seen in our specimen was the most severe in our entire material. This fact lends support for Schuknecht and Gross's opinion[36] that the atrophy is the cause for the basilar membrane rupture. The large cyst-like spaces in the atrophic ligament are similar to those described by Kelemen and Linthicum[6] and others. Figure 8 in Altmann's paper of 1966[4] demonstrates in a cross-section a situation which is identical with the finding in the middle and apical turn in our specimen. The ligament is markedly atrophic, enclosing a large empty space, and it appears as if the basilar membrane was pulled down by the ligament toward the scala tympani. The question of the effect of visible distortion and ruptures of the basilar membrane is mostly academic, since it occurs in labyrinths where sensorineural degeneration and hearing loss are already severe. A rupture of the basilar membrane will cause mingling of endolymph and perilymph, which will probably destroy what remains of the sensory cells.[87,88]

If one subscribes to the hypothesis that atrophy of the spiral ligament can indeed lead to sagging or even to rupture of the basilar membrane, an important question arises: Can mild atrophy of the spiral ligament, occurring to some degree in virtually all temporal bones from older patients,[24,34,37] or alteration in the basilar membrane itself bring about what Schuknecht[89] has termed "mechanical presbyacusis"? Although v. Békésy[90] found that he could not easily create tension in the basilar membrane experimentally, he has mentioned that he produced a local slackening of the membrane in a human cochlea postmortem by pushing and displacing the spiral ligament. His "careful measurements showed that this bending of the basilar membrane had not the slightest effect either on the distribution of the amplitude of the vibration or on the distribution of phase as measured with the phase stroboscope." Precise physical measurements of the compliance of the basilar membrane in young and old ears might answer the question, but interpretation of such a study must always be guarded because of preparation artifacts and postmortem changes.

The pair of bones with the most extensive otosclerotic process, Case 2, showed an almost complete bilateral loss of sensory cells in the entire vestibular system. An additional specimen with multiple foci, Case 4, showed complete absence of sensory cells on the cristae, while macular hair cells were still present. Such specimens provide a warning against the popular label "dead labyrinth" in cases of absent caloric responses (Fig. 21).

The loss of planum semilunatum and "dark cells" in the former bones is an interesting observation, comparable to strial atrophy in the cochlea. Similar loss of dark cells was recently observed by Sando et al.[43] The atrophy of dark cells is, however, difficult to evaluate. It can occur with aging and with various forms of vestibular pathology,[91] and therefore should not be considered specific to otosclerosis. The hair cell loss in the vestibular system may have been caused directly by bone pathology or may have been secondary to atrophy of the planum and the dark cells. Lindsay and Beal[8] have pointed out that the endosteum in the vestibular system is less susceptible to the irritating effect of active otosclerosis than the endosteum facing the spiral ligament and scala tympani. In general it appears that the vestibular tissues may be less likely to be directly influenced by bone pathology perhaps because of that fact or because the membranous labyrinth, with the exception of the saccule, does not lie in as close contact with the osseous labyrinth in its vestibular portion as it does in the cochlea. In Cases 1 and 3 where the focus extended to the horizontal and superior ampullae, no obvious changes were seen in the membranous labyrinth which could be related to otosclerosis. Like Kelemen and Linthicum,[6] but unlike Sando et al,[43] we found no selective degeneration of the superior branch of the vestibular nerve, despite extensive involvement of the bone around the nerve in Case 1 and in the group of specimens with multiple foci. The finding is in agreement with Siebenmann's original concept that otosclerosis does not attack the vestibular nerve.[27]

The history of vertiginous attacks and the finding of severe unilateral hydrops labyrinthi, plus a mild hydrops on the opposite side in Case 3 is strongly suggestive of Menière's disease. Whether the hydrops was secondary to otosclerosis or just a coincidental finding is unclear. The endolymphatic duct and sac were not examined in this specimen. Another explanation for disequilibrium in otosclerotics could be an altered composition and density of the vestibular fluids,[27] causing an ampullary disfunction by disturbing the neutral buoyancy of the cupulae.[92]

Fenestration is still performed occasionally and may also occur as a surgical complication or as a result of chronic middle ear infection with cholesteatoma. It was therefore of interest to observe severe vestibular degeneration in two of the four temporal bones from patients who had undergone fenestration. This is well in agreement with electronystagmographic observations of fenestrated patients, many of whom have a reduced response from the operated ear, often with indications of selective damage to the crista of the horizontal canal.[93] In our limited material the damage affected more or less equally all ampullae and the utricle. The degree of damage appeared to be related to the extent of tissue reaction at the fenestra.

The vestibular degeneration probably occurred as the result of a disturbed homeostasis in the vestibular system. The membranous walls of the semicircular canals and in all likelihood those of the rest of the vestibular membranous labyrinth, not only separate perilymph from endolymph, but participate actively, like Reissner's membrane, in maintaining the specific ionic composition of the endolymph that is essential for the function and survival of the vestibular sensory epithelia.[94] A surgical rupture of Reissner's membrane allows perilymph to enter the scala media and causes local hair cell loss.[87,88] Similarly in the vestibular system any mechanical damage to the membranous labyrinth is likely to alter the function of the membranous walls or to create openings that allow labyrinthine fluids to mix and bring about a secondary hair cell degeneration. The severe vestibular degeneration seen in Case 5 (Figs. 11, 22), admittedly many years after operation, shows that the old fenestration approach for destructive labyrinthectomy can be fairly effective.

The fistula in the saccular duct of a patient who had undergone stapedectomy is an unexpected finding, difficult to explain (Fig. 23). The surgery was performed by an experienced stapes surgeon, and there were no known complications during or after the procedure. Surprisingly, this fistula seems to have caused very little harm to sensory structures. Certainly there must have been some mixing of endolymph and perilymph, but perhaps a slow "longitudinal flow"[88] of fluids toward the endolymphatic sac prevented ionic changes sufficient to interfere with the hair cells. Not even the macula sacculi showed more hair cell degeneration than one would have expected in a patient of this age. The finding could be coincidental, but it is unique. We have not observed anything similar in any of our other material.

SUMMARY

Twenty-four temporal bones from patients with otosclerosis were studied by the method of microdissection and surface preparations. During the removal of the otic capsule, otosclerotic foci were clearly seen. They differed in color and texture from the capular bone, and their state of activity could be judged by variations in their consistency and vascularity. All specimens had an ankylotic stapes or had undergone stapedectomy.

Small anterior foci constituted the most common form of involvement of the otic capsule. All were judged to have been inactive at the time of death. Although none of them appeared to have caused obvious sensorineural degeneration, the difficulty of making such an evaluation without extensive quantitative analysis is recognized. Almost all human temporal bones show various degrees of sensorineural change in the lower basal turn. No cases of "pure cochlear otosclerosis" were seen, i.e., sensorineural degeneration secondary to one or more otosclerotic lesions, without stapes ankylosis and conductive hearing loss.

Large anterior foci which reached the upper basal turn did tend to cause sensorineural degeneration. The left temporal bone from an 83-year-old man with a large and active focus extending as far as the apical turn was particularly revealing. The specimen displayed a circumscribed sensorineural degeneration in the upper basal turn, where there was an almost exact correspondence between the location and extent of the lesion and that of the otosclerotic bone impinging upon the three scalae. No such degeneration was seen in the apical turn, where the process did not involve scala tympani.

It is postulated that a toxic factor had diffused from the focus and acted directly on Corti's organ, rather than indirectly by altering the function of other cochlear tissues. The upper basal turn could represent a site of predilection for sensorineural degeneration in capsular otosclerosis, since an anterior focus so commonly expands into this region. A specific audiometric pattern with a low-frequency "dip" may be characteristic of such cases.

When two or more foci were present at least one of the foci was always poorly defined, and the otosclerotic process involved the round window and the cochlear aqueduct, usually causing severe obstruction of both. Most of these specimens also had new bone formation in scala tympani. All but one demonstrated extensive and severe sensorineural degeneration. One pair of temporal bones showed a circumscribed lesion occluding the round window in addition to the ankylosis of the stapes.

In three specimens huge vessels were observed to connect the otosclerotic foci with the cochlear vasculature, and similar shunts, but of normal capillary size, were observed in two others. The former specimens displayed unusual cochlear vascular pathology, mainly in the form of severe vasodilation, suggesting that the shunts may have altered the cochlear circulation. Severe involvement of the endosteum of scala tympani caused loss of small vessels in that region. In some of the cases with multiple foci, strial atrophy and atrophy or fibrotic change in the spiral ligament were observed. One of these temporal bones which had the most severe atrophy of the spiral ligament seen in our entire human material had multiple holes in the basilar membrane. Severe sensorineural degeneration of the entire vestibular system was seen in one pair of temporal bones with multiple otosclerotic foci. Furthermore, of four specimens from fenestrated patients, two showed extensive and severe vestibular pathology. In one of these there was a total loss of hair cells from the ampullar cristae, but scattered hair cells remained on the maculae of the utricle and saccule. In one specimen from a stapedectomized patient, a fistula of the saccular duct was present.

A severe cochleosaccular hydrops was found in one specimen with multiple otosclerotic foci. It was not clear whether this condition was coincidental or was related to the otosclerosis.

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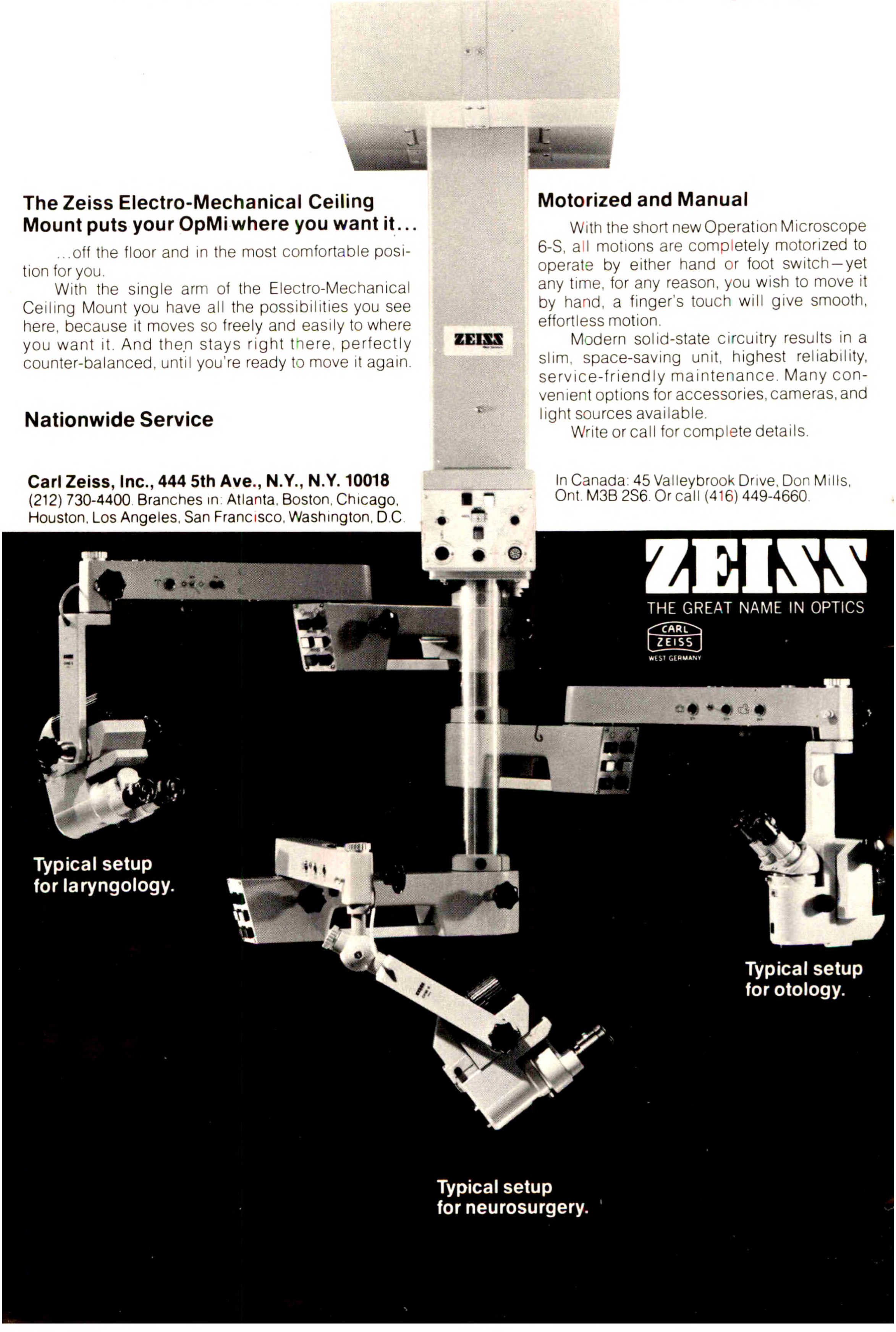

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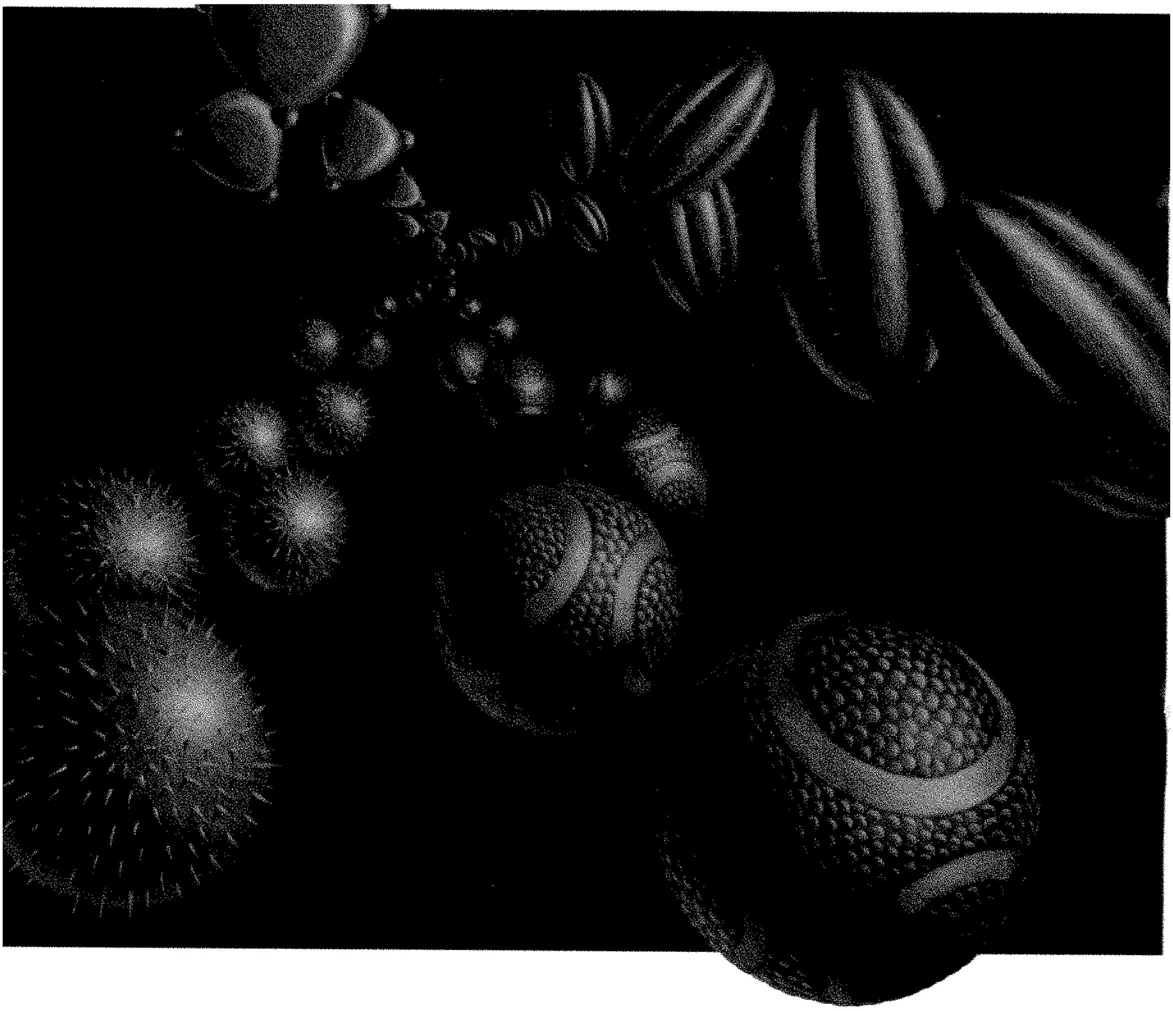

ALLERGENS CHANGE WITH THE SEASONS.
THE RHINITIS THEY CAUSE DOESN'T.

Available on your Rx only, ACTIFED Tablets deliver 60 mg of SUDAFED (pseudoephedrine HCl), the orally effective decongestant, and 2.5 mg of ACTIDIL (triprolidine HCl), the potent antihistamine discovered in the Wellcome Research Laboratories. Together, they help relieve the tearing, sneezing and stuffiness of allergic and vasomotor rhinitis* and the common cold**—summer, winter, anytime.

And anyplace: chosen for the original Apollo flights, ACTIFED was also in orbit on the Apollo/Soyuz mission.

Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
*"Probably" effective: For the symptomatic treatment of seasonal and perennial allergic rhinitis and vasomotor rhinitis.
**"Lacking substantial evidence of effectiveness as a fixed combination": For the prophylaxis and treatment of the symptoms associated with the common cold.
Final classification of the less-than-effective indications requires further investigation.

Warning: *Use in Pregnancy:* Experience with this drug in pregnant women is inadequate to determine whether there exists a potential for harm to the developing fetus.

Precautions: Although pseudoephedrine hydrochloride is virtually without pressor effect in normotensive patients, it should be used with caution in patients with hypertension. In addition, even though triprolidine hydrochloride has a low incidence of drowsiness, appropriate precautions should be observed.

Adverse reactions: The great majority of patients will exhibit no side effects. However, certain patients may exhibit mild stimulation or mild sedation—no serious side effects have been noted.

Complete literature available
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For symptomatic relief of allergic rhinitis* whatever the season

ACTIFED® TABLETS

Each scored tablet contains ACTIDIL® (triprolidine HCl) 2.5 mg and SUDAFED® (pseudoephedrine HCl) 60 mg.

The potent antihistamine/decongestant tablet—with convenient t.i.d. dosage for adults

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All-day, all-night relief when she's dogged by allergies

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(tripelennamine HCl)

sustained-release tablets 100 mg

Teary eyes. Stuffy head. tchy skin. The symptoms he's picked up from her four-footed allergenic friend have her leading a dog's life, too.

PBZ-SR can help subdue these offenders because it provides tripelennamine—one of the most effective antihistamines available.

Wax matrix releases PBZ slowly

The inert wax matrix releases medication gradually as it passes through the G.I. tract. Each tablet provides sustained release of medication for all-day, all-night relief on a b.i.d. schedule.

Minimizes risk of sedation

Sustained-release action helps minimize the problem of sedation. However, patients should be warned about engaging in activities requiring mental alertness, such as driving a car, operating machinery, or using hazardous appliances. Unlike many other antihistamines, small easy-to-take PBZ-SR tablets leave no aftertaste.

PBZ-SR®
(tripelennamine HCl)
sustained-release tablets

INDICATIONS
Perennial and seasonal allergic rhinitis; vasomotor rhinitis; allergic conjunctivitis due to inhalant allergens and foods; mild, uncomplicated allergic skin manifestations of urticaria and angioedema; amelioration of allergic reactions to blood or plasma; dermographism; anaphylactic reactions as adjunctive therapy to epinephrine and other standard measures after the acute manifestations have been controlled.

CONTRAINDICATIONS
Pyribenzamine should not be used in premature infants, neonates, or nursing mothers; patients receiving MAO inhibitors; patients with narrow angle glaucoma, stenosing peptic ulcer, symptomatic prostatic hypertrophy, bladder neck obstruction, pyloroduodenal obstruction, lower respiratory tract symptoms (including asthma), or hypersensitivity to tripelennamine or related compounds.

WARNINGS
Antihistamines often produce drowsiness and may reduce mental alertness in children and adults. Patients should be warned about engaging in activities requiring mental alertness (eg, driving a car, operating machinery or hazardous appliances). In elderly patients, approximately 60 years or older, antihistamines are more likely to cause dizziness, sedation and hypotension. Patients should be warned that the central nervous system effects of Pyribenzamine may be additive with those of alcohol and other CNS depressants (eg, hypnotics, sedatives, tranquilizers, antianxiety agents).
Antihistamines may produce excitation, particularly in children.

Usage in Pregnancy
Although no Pyribenzamine-related teratogenic potential or other adverse effects on the fetus have been observed in limited animal reproduction studies, the safe use of this drug in pregnancy or during lactation has not been established. Therefore, the drug should not be used during pregnancy or lactation unless, in the judgment of the physician, the expected benefits outweigh the potential hazards.

Usage in Children
In infants and children particularly, antihistamines in overdosage may produce hallucinations, convulsions and/or death.

PRECAUTIONS
Pyribenzamine, like other antihistamines, has atropine-like, anticholinergic activity and should be used with caution in patients with increased intraocular pressure, hyperthyroidism, cardiovascular disease, hypertension, or history of bronchial asthma.

ADVERSE REACTIONS
The most frequent adverse reactions to antihistamines are sedation or drowsiness; sleepiness; dryness of the mouth, nose, and throat; thickening of bronchial secretions; dizziness; disturbed coordination; epigastric distress.
Other adverse reactions which may occur are: fatigue; chills; confusion; restlessness; excitation; hysteria, nervousness; irritability; insomnia; euphoria; anorexia; nausea; vomiting; diarrhea; constipation; hypotension; tightness in the chest; wheezing; blurred vision; diplopia; vertigo; tinnitus; convulsions; headache; palpitations; tachycardia; extrasystoles; nasal stuffiness; urinary frequency; difficult urination; urinary retention; leukopenia; hemolytic anemia; thrombocytopenia; agranulocytosis; aplastic anemia; allergic or hypersensitivity reactions, including drug rash, urticaria, anaphylactic shock, and photosensitivity. Although the following may have been reported to occur in association with some antihistamines, they have not been known to result from the use of Pyribenzamine: excessive perspiration, tremor, paresthesias, acute labyrinthitis, neuritis and early menses.

C77-20 Rev. 8/77

Before starting therapy, consult complete product literature.

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Division of CIBA-GEIGY Corporation
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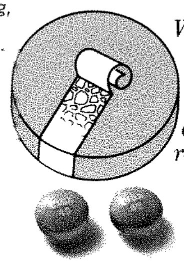

Wax matrix assures slow release of PBZ...b.i.d. dosage provides all-day, all-night relief.

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for evoked response measurements in situations where the use of conventional behavioral audiometry is not practical.

Evoked response measurement protocols are especially useful for patients who are unable to accurately describe their sensory experiences because they are infants, retarded, comatose, suffer neurological disorders or are normal, but anxious.

Auditory evoked response measurements involve the use of click or tone burst stimuli (at various intensities, rates, durations and frequencies) which are used to noninvasively record electrical activity along the auditory pathway.

Some typical applications include:

- **Brainstem auditory evoked responses using click stimuli for hearing evaluations, to determine conductive versus sensorineural hearing loss and to localize acoustic tumors, demyelinating disorders and vascular lesions.**
- **Middle or late latency components measurements using tone burst stimuli to check specific cortical responses over a wide range of frequencies.**
- **Electrocochleography using click or tone burst stimuli to evaluate conductive hearing loss.**

The result of an auditory evoked response measurement is a precise waveform where the elements of interest are the amplitude, latency and morphology under known stimulus conditions giving the clinician a valuable tool for diagnosing hearing problems.

The CA-1000 is a complete portable system including stimulus generators, acoustically shielded headphones, recording electrodes, preamplifier, signal averaging computer with built-in oscilloscope display including accurate numerical readout of latency and amplitude, recorder for permanent records and a convenient equipment cart.

For complete details on the CA-1000 system or to arrange a demonstration please phone or write Nicolet.

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Telephone: 608/271-3333

References
Brackmann, D., Selters, W.A. 1977. Acoustic tumor detection with brainstem electric response audiometry. **Archives of Otolaryngology** 103:181-7.
Hecox, K. and Galambos, R. Brainstem auditory evoked responses in human infants and adults. **Archives of Otolaryngology,** 1974, 99: 30-33
Jewett, D. and Williston, J. Auditory-evoked far-fields averaged from the scalp of humans. **Brain,** 1971, 94: 681-696.
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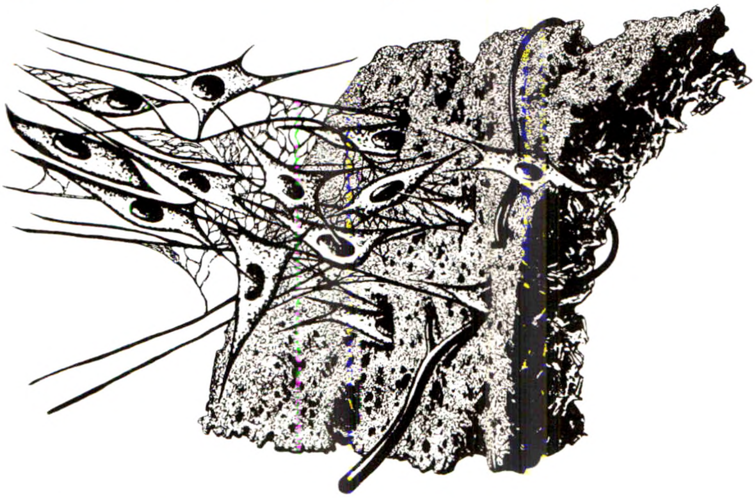

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** Summary of clinical data and extensive bibliography are available on request.*

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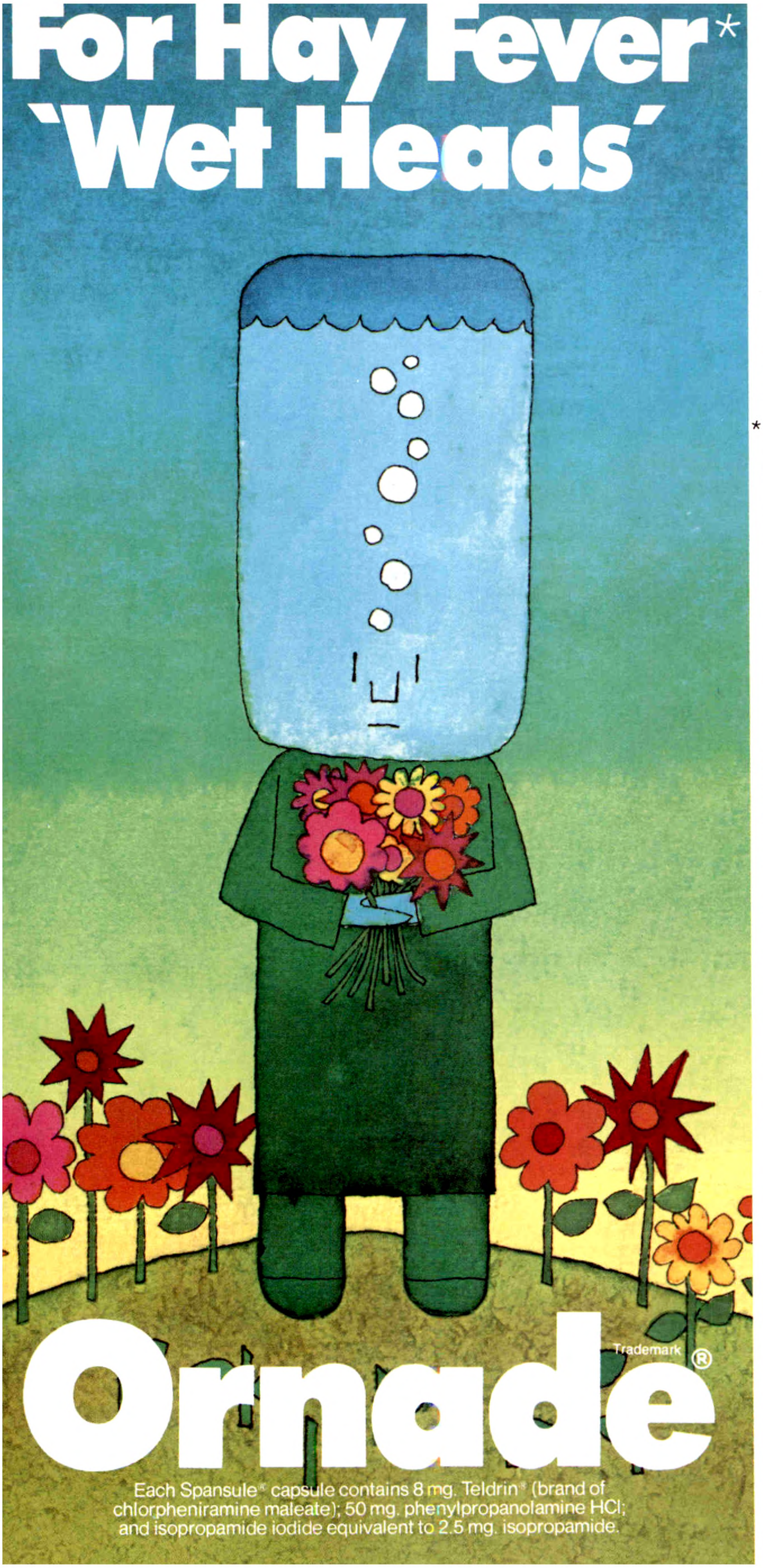

Each Spansule* capsule contains 8 mg. Teldrin* (brand of chlorpheniramine maleate); 50 mg. phenylpropanolamine HCl; and isopropamide iodide equivalent to 2.5 mg. isopropamide.

Relieves the symptoms

stuffiness
runniness
sneeziness
weepiness

Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

* **Indications**

Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information FDA has classified the indication as follows:

Possibly effective: For relief of upper respiratory tract congestion and hypersecretion associated with vasomotor rhinitis an allergic rhinitis, and for prolonged relief.

Lacking in substantial evidence of effectiveness: For relief of nasal congestion and hypersecretion associated with the common cold and sinusitis.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Hypersensitivit to any component; concurrent MA inhibitor therapy; severe hyperten sion; bronchial asthma; coronary artery disease; stenosing peptic ulcer; pyloroduodenal or bladder neck obstruction. Children under 6

Warnings: Caution patients about activities requiring alertness (e.g., operating vehicles or machinery). Warn patients of possible additive effects with alcohol and other CNS depressants.

Usage in Pregnancy: In pregnancy nursing mothers and women who might bear children, weigh potenti benefits against hazards. Inhibition of lactation may occur.

Effect on PBI Determination and I Uptake: Isopropamide iodide may alter PBI test results and will suppr I^{131} uptake. Substitute thyroid tests unaffected by exogenous iodides.

Precautions: Use cautiously in persons with cardiovascular disease, glaucoma, prostatic hypertrophy, hyperthyroidism.

Adverse Reactions: Drowsiness; excessive dryness of nose, throat or mouth; nervousness; or insomni Also, nausea, vomiting, epigastric distress, diarrhea, rash, dizziness, weakness, chest tightness, angina pain, abdominal pain, irritability, palpitation, headache, incoordination, tremor, dysuria, difficulty in urination, thrombocytopenia, leukopenia, convulsions, hypertension, hypotension, anorexia, constipation, visual disturbances, iodine toxicity (acne, parotitis).

Supplied: Bottles of 50 and 500 capsules; in Single Unit Packages 100 (intended for institutional use only).

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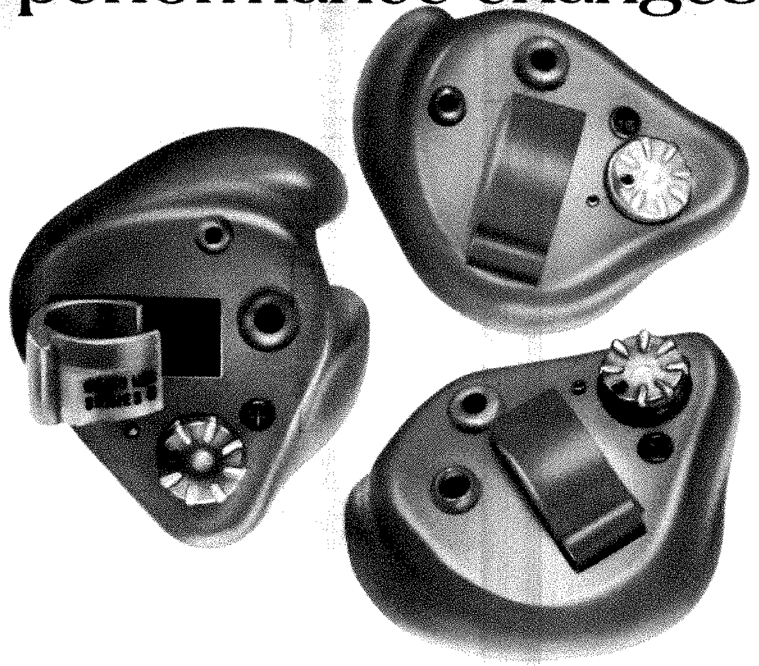
The Maico Series R. Two adjustment controls standard — for on-the-spot performance changes.



Every Series R instrument comes from Maico complete with two continuously variable controls. One for power range adjustment and the other for low frequency modification. These controls help you to correctly modify the electroacoustic performance of the aid to the user's requirements, on-the-spot.

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- Newly designed extra thick volume control with raised serrations — for ease of rotation.
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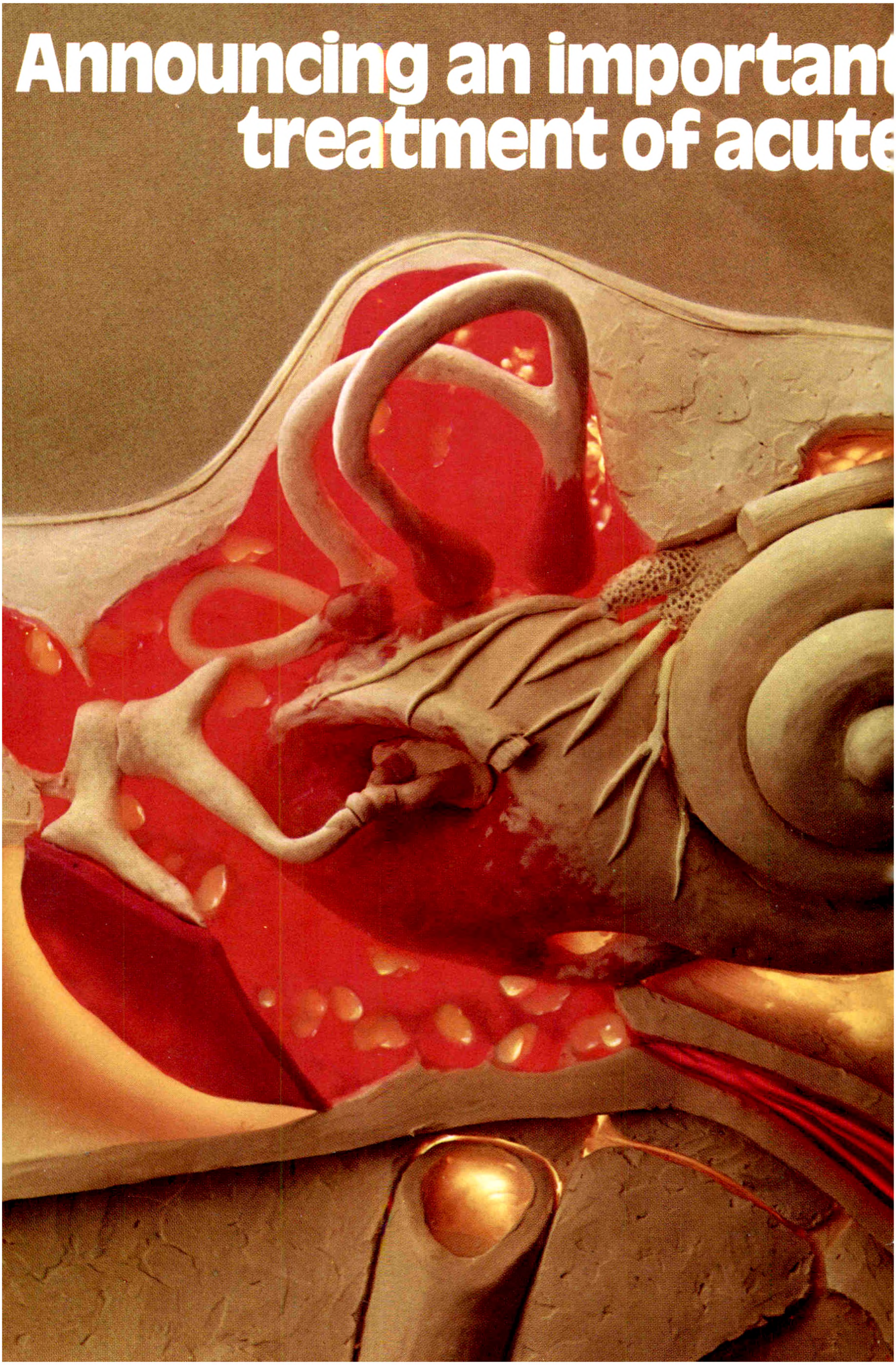
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Now indicated when, in the judgment of the physician, it offers an advantage over other antimicrobial agents

actrim demonstrates 93% success rate in multicenter studies

High efficacy against major otic pathogens

Bactrim is highly effective against acute otitis media caused by *Str. pneumoniae (D. pneumoniae)* or *H. influenzae.* An overall efficacy of 93% was reported in a multicenter evaluation* of 121 patients with acute otitis media due to these organisms. The age range was 2 months to 13 years, with an average of 3 years.

Usual in vitro spectrum includes ampicillin-resistant strains of H. influenzae

Note: Limited clinical information is presently available on the effectiveness of treatment of acute otitis media with Bactrim when the infection is due to *H. influenzae* resistant to ampicillin.

Useful in patients allergic to penicillins

Same safety profile as in other indications

In pooled data* on 238 patients receiving Bactrim for an average of approximately 10 days, adverse effects were infrequent and not serious. Although serious reactions can occur, none were noted in these studies. Contraindications to Bactrim include patients hypersensitive to its components and infants less than two months of age.

Note: Bactrim should not be used in the treatment of streptococcal pharyngitis, since the incidence of failure has been greater than that of penicillin in eradicating group A beta-hemolytic streptococci from the tonsillopharyngeal area.

*Data on file, Medical Department, Hoffmann-La Roche Inc.

Bactrim™ Suspension

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(40 mg trimethoprim and 200 mg sulfamethoxazole per 5 ml)

Convenient b.i.d. therapy

Please see following page for summary of product information.

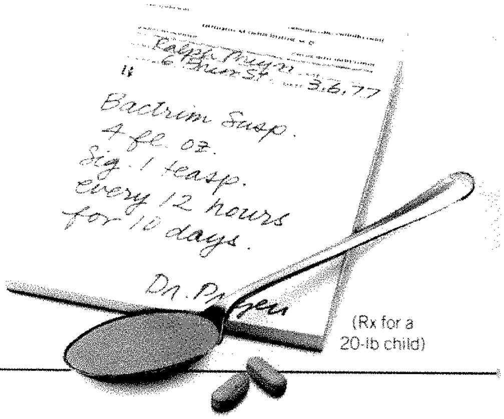
A major nonpenicillin now indicated for acute otitis media in children

Bactrim™

Suspension Pleasant fruit-licorice flavor
Each teaspoonful (5 ml) contains
40 mg trimethoprim and 200 mg sulfamethoxazole.

Tablets Small, easily swallowed, scored
Each tablet contains 80 mg trimethoprim and
400 mg sulfamethoxazole.

Convenient b.i.d. therapy



(Rx for a 20-lb child)

Before prescribing, please consult complete product information, a summary of which follows:

Indications and Usage: For the treatment of urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli, Klebsiella-Enterobacter, Proteus mirabilis, Proteus vulgaris, Proteus morganii.* It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination. *Note:* The increasing frequency of resistant organisms limits the usefulness of all antibacterials, especially in these urinary tract infections.

For acute otitis media in children due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in physician's judgment it offers an advantage over other antimicrobials. Limited clinical information presently available on effectiveness of treatment of otitis media with Bactrim when infection is due to ampicillin-resistant *Haemophilus influenzae.* To date, there are limited data on the safety of repeated use of Bactrim in children under two years of age. Bactrim is not indicated for prophylactic or prolonged administration in otitis media at any age.

Also for the treatment of documented *Pneumocystis carinii* pneumonitis. To date, this drug has been tested only in patients 9 months to 16 years of age who were immunosuppressed by cancer therapy.

Contraindications: Hypersensitivity to trimethoprim or sulfonamides; pregnancy; nursing mothers; infants less than two months of age.

Warnings: BACTRIM SHOULD NOT BE USED TO TREAT STREPTOCOCCAL PHARYNGITIS. Clinical studies show that patients with group A β-hemolytic streptococcal tonsillopharyngitis have higher incidence of bacteriologic failure when treated with Bactrim than do those treated with penicillin. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides. Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended; therapy should be discontinued if a significantly reduced count of any formed blood element is noted.

Precautions: Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In patients with glucose-6-phosphate dehydrogenase deficiency, hemolysis, frequently dose-related, may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim. *Blood dyscrasias:* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic reactions:* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal reactions:* Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis. *CNS reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous reactions:* Drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia in patients; cross-sensitivity with these agents may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies.

Dosage: Not recommended for infants less than two months of age.

URINARY TRACT INFECTIONS IN ADULTS AND CHILDREN AND ACUTE OTITIS MEDIA IN CHILDREN:

Adults: Usual adult dosage for urinary tract infections—1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 10-14 days.

Children: Recommended dosage for children with urinary tract infections or acute otitis media—8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, in two divided doses for 10 days. A guide follows:

Children two months of age or older:

Weight		Dose—every 12 hours	
lbs	kgs	Teaspoonfuls	Tablets
20	9	1 teasp. (5 ml)	½ tablet
40	18	2 teasp. (10 ml)	1 tablet
60	27	3 teasp. (15 ml)	1½ tablets
80	36	4 teasp. (20 ml)	2 tablets or 1 DS tablet

For patients with renal impairment:

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Usual standard regimen
15-30	½ the usual regimen
Below 15	Use not recommended

PNEUMOCYSTIS CARINII PNEUMONITIS: Recommended dosage: 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours in equal doses every 6 hours for 14 days. See complete product information for suggested children's dosage table.

Supplied: *Double Strength (DS) tablets,* each containing 160 mg trimethoprim and 800 mg sulfamethoxazole, bottles of 100; Tel-E-Dose® packages of 100; Prescription Paks of 20. *Tablets,* each containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 40, available singly and in trays of 10. *Oral suspension,* containing in each teaspoonful (5 ml) the equivalent of 40 mg trimethoprim and 200 mg sulfamethoxazole, fruit-licorice flavored—bottles of 16 oz (1 pint).

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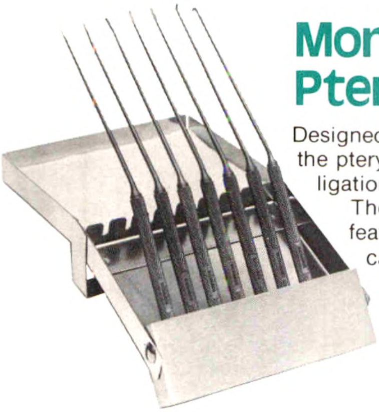
* Hamilton S. Dixon, M.D., Rome, Georgia



Montgomery[†] Pterygomaxillary Instruments

Designed for the surgical technique of the transantral approach to the pterygomaxillary fossa, these stainless steel instruments allow ligation of the maxillary artery or sectioning of the Vidian nerve. They are also ideal for use in antrostomies. The instruments feature a velvet vapor blast finish. A book-fold stainless steel case protects delicate points during autoclaving and handling. Instruments stand up for access during surgery.

[†] William W. Montgomery, M.D., Boston, Massachusetts

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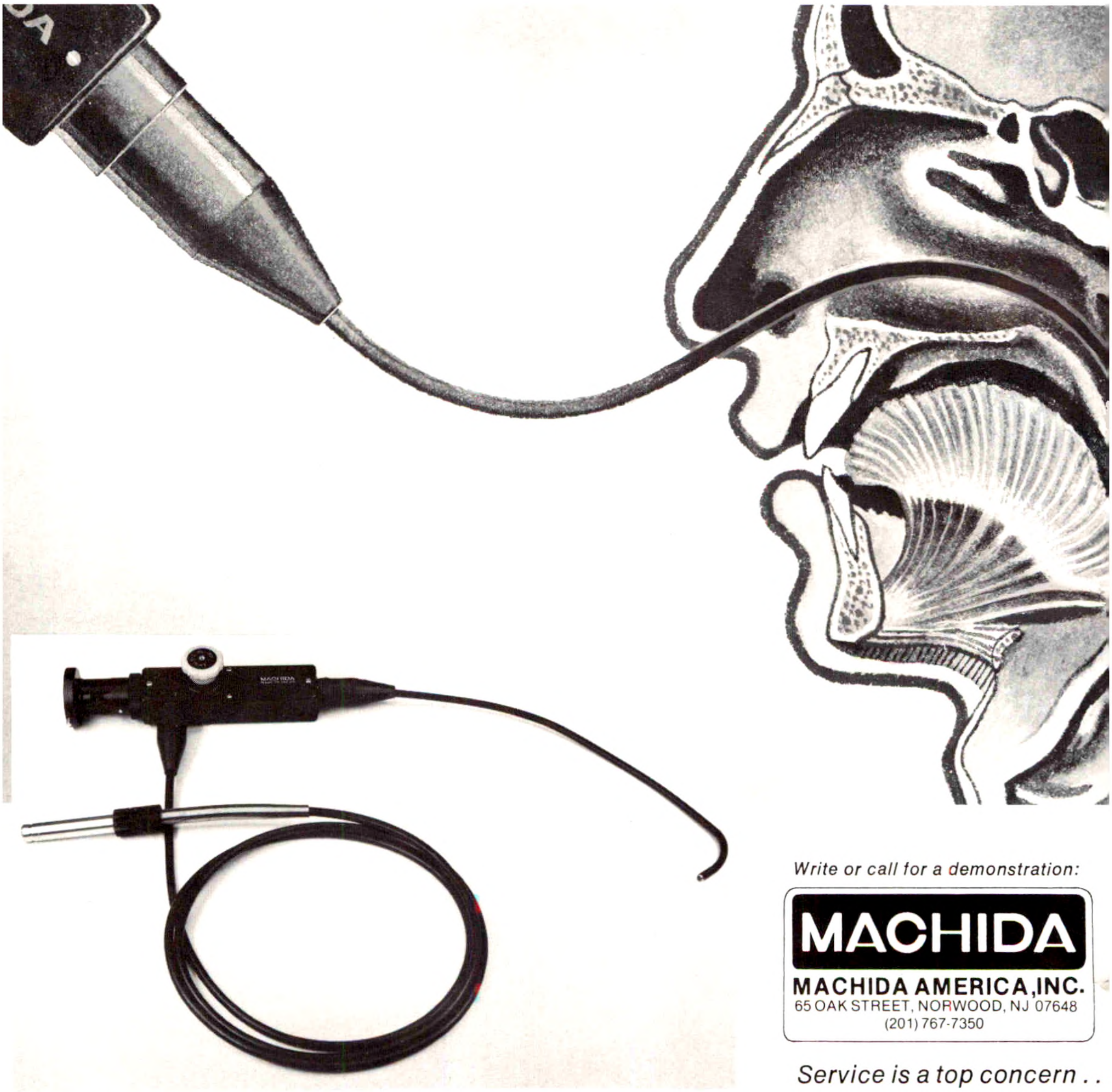

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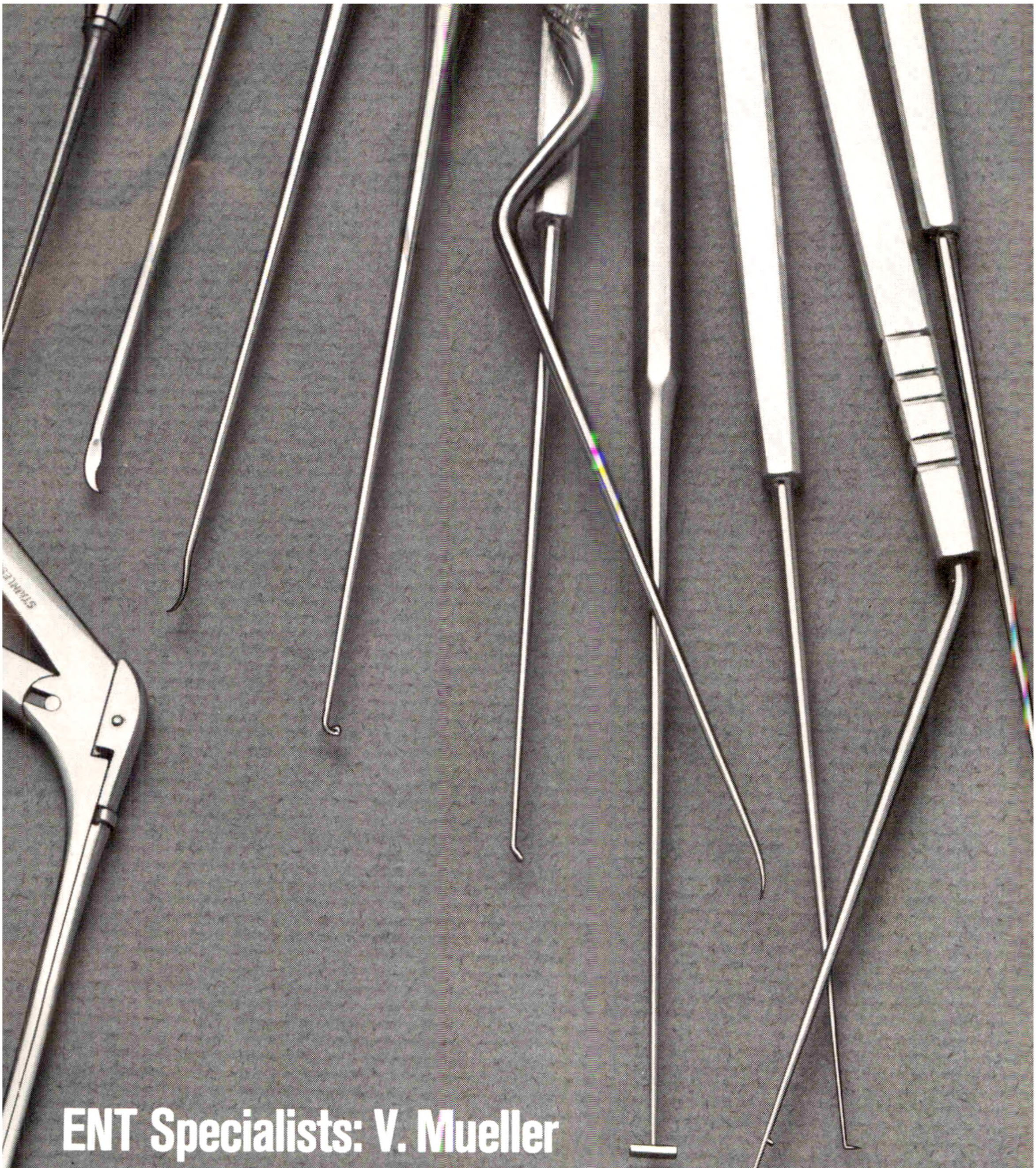

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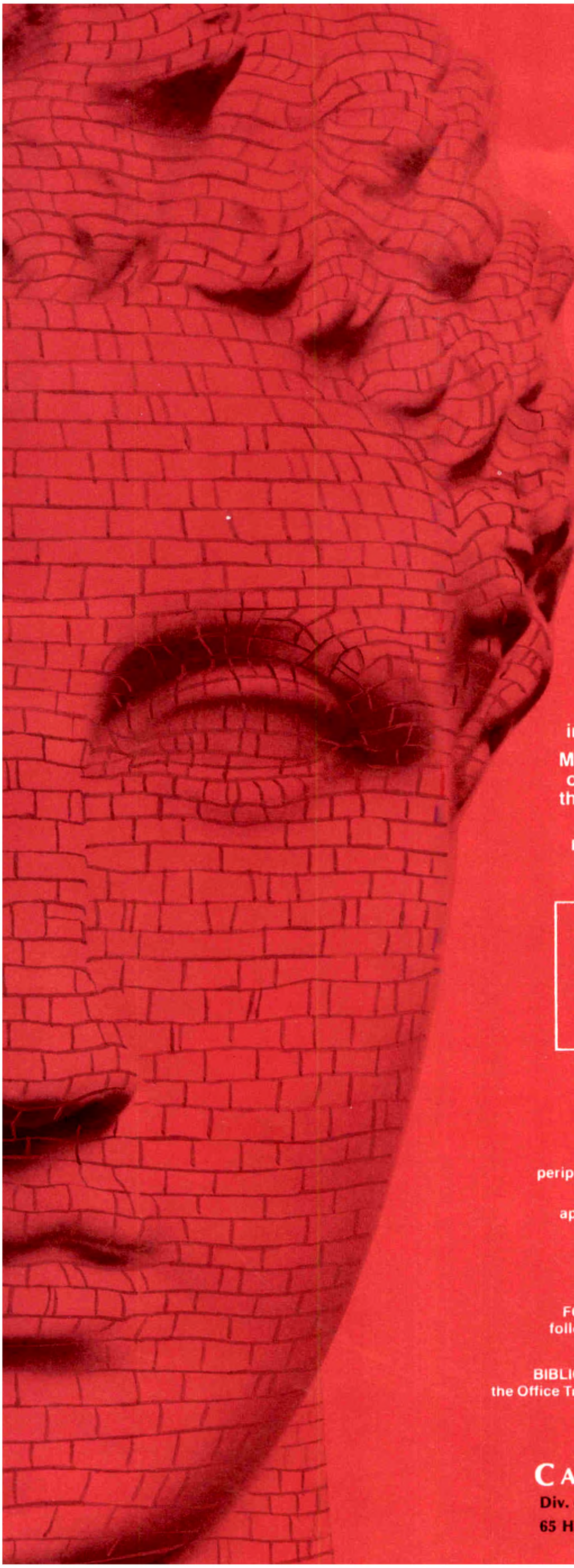

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For the overlapping symptoms of tension *and* vascular headaches

Midrin provides relief for the "overlapping maze" of painful symptoms common to tension, migraine and other vascular headaches. The Midrin formulation allows greater prescribing latitude for headaches and is of particular value where ergotamine is contraindicated or cannot be tolerated.

Midrin relieves headache pain with three distinct and separate actions:

Isometheptene, a sympathomimetic amine, constricts the caliber of the blood vessels in the cerebral area. The action is similar to ergotamine[1] but possessed of a lower order of toxicity.

Dichloralphenazone, a sedative, helps to calm the anxious patient, reducing the emotional stress which often precipitates and intensifies the headache.

Acetaminophen reduces the perception of pain impulses originating from dilated cerebral vessels.

Midrin with its effective, prompt action and absence of significant toxicity can provide a valuable tool in the routine treatment of tension, migraine and other vascular headaches.

EACH MIDRIN CAPSULE CONTAINS: Isometheptene Mucate 65 mg., Dichloralphenazone 100 mg. and Acetaminophen 325 mg. INDICATIONS: For relief of vascular and tension headaches.

Based on a review for this drug (Isometheptene Mucate), the National Academy of Sciences-National Research Council and/or other information, FDA has classified the other indication as "Possibly" effective in the treatment of migraine headache. Final classification of the less-than-effective indication requires further investigation.

CONTRAINDICATIONS: Glaucoma and/or severe cases of: renal disease, hypertension, organic heart disease, hepatic disease and in those patients who are on monoamine-oxidase inhibitor therapy.

PRECAUTIONS: Caution should be observed in hypertension, peripheral vascular disease and after recent cardiovascular attacks.

ADVERSE REACTIONS: Transient dizziness and skin rash may appear in hypersensitive patients. This can usually be eliminated by reducing the dose.

USUAL ADULT DOSAGE:
FOR RELIEF OF TENSION HEADACHE — One or two capsules every four hours up to 8 capsules a day.

FOR RELIEF OF MIGRAINE HEADACHE — Two capsules at once, followed by one capsule every hour until relieved, up to 5 capsules within a twelve hour period.

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Ann Otol 87:1978

FURTHER OBSERVATIONS ON POSTERIOR AMPULLARY NERVE TRANSECTION FOR POSITIONAL VERTIGO

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SUMMARY — An evaluation was made on ten patients with benign paroxysmal positional vertigo (BPPV) in whom transection of the posterior ampullary nerve was performed by the middle ear approach under local anesthesia. The undermost ear in the provocative test position was selected for surgery. All ten patients were relieved of positional vertigo by the procedure. Of the five patients who were relieved of BPPV by posterior ampullary nerve transection prior to 1974, the long-term follow-up on four revealed continued relief of vertigo. Five additional patients treated by this surgical procedure since 1975 have also experienced relief from BPPV, but a moderate sensorineural hearing loss occurred in one patient. Two additional patients with BPPV were explored surgically but the singular canal could not be located. Persistence of the vertigo in these two patients strengthens the conclusion that the posterior semicircular canal sense organ is largely responsible for BPPV.

This report represents an up-to-date evaluation of posterior ampullary nerve (PAN) transection as a treatment for benign paroxysmal positional vertigo (BPPV). Three groups of patients with incapacitating BPPV are included in this study. The first group contains five patients described in 1974 who were relieved of positional vertigo by PAN transection.[1] The second group is made up of five additional patients who were operated upon since the 1974 report. The third group consists of two patients with BPPV in whom surgical exploration of the round window niche without PAN transection was carried out. The persistence of positional vertigo in these last two patients represents a control of the effectiveness of PAN transection.

Long-term evaluation on four of the original five patients was obtained. The follow-up interval in these four patients ranged from two to four years. Two patients were examined by the author and the evaluation on two others was reported by the referring otolaryngologists. One patient could not be located. All four patients have remained free of BPPV and their hearing levels are unchanged from the levels recorded in 1974. The unsteadiness resulting from the partial labyrinthectomy has disappeared.

An additional group of five patients with disabling BPPV have had PAN transection in the years 1975 through 1977. The preoperative findings in these five patients are contained in Table 1 and demonstrate the objective criteria for the diagnosis of BPPV. The undermost ear in the provocative test position was considered responsible for BPPV and was selected for surgery. The surgical approach to the singular canal was identical to that described in 1974 except for a modification employed in the last three patients of this group. Since sensorineural hearing loss has occurred even when exposure of the singular canal was technically satisfactory (Fig. 1), the approach was altered so that the inferior rather than the lateral aspect of the canal was opened by drilling in the floor of the round window niche (Figs. 2, 3). This change in the location of the drilling site preserved a wider bony ridge adjacent to the round window membrane in order to protect the nearby basal turn of the cochlea. All five patients were immediately relieved of their positional vertigo following transection of the PAN (Table 2). The follow-up evaluation of these five pa-

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TABLE 1. FINDINGS IN PATIENTS WITH BENIGN PAROXYSMAL POSITIONAL VERTIGO (BPPV)

			Nystagmus				
Patient	*Ear Inv.*	*Duration BPPV (yr)*	*Lat. (Sec)*	*Dur. (Sec)*	*Type*	*Rev.*	*Fat.*
G. C. 52F	L	4	3	20	CW	+	+
J. O. 47M	L	3	2	20	CW	+	+
A. L. 45M	L	1	4	25	CW	+	+
D. S. 35M	R	1	3	22	CCW	+	+
M. L. 35M	R	30	3	25	CCW	+	+

CW - Clockwise; CCW - Counterclockwise; Lat. - Latency; Dur. - Duration; Rev. - Reversible; Fat. - Fatigable; Inv. - Involved.

tients ranged from two years to two months.

In two additional patients with BPPV, surgical exploration of the round window niche was carried out but the singular canal could not be located despite extensive drilling. These patients did not experience vertigo during the procedure, indicating that the singular canal was not entered. Since our previous experience revealed that the singular canal may sometimes be inaccessibly located under the basal turn of the cochlea, exposure of the canal in this location from the middle ear approach would probably incur a severe sensorineural hearing loss. After conference with the patients, the surgical attempts at PAN transection were aborted. One of these patients was a 61-year-old housewife who had BPPV for seven years. The second patient was a 60-year-old woman who had BPPV for a one-year period. Both patients continued to experience positional vertigo following the surgical exploration. No hearing loss occurred as a result of surgical exploration in these two patients.

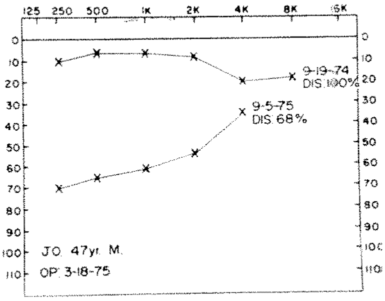

Fig. 1. Hearing test on patient J.O. demonstrating the sensorineural hearing loss resulting from surgery on 3-18-75.

DISCUSSION

The results in these patients indicate that posterior ampullary nerve transection is consistently effective in the relief of benign paroxysmal positional vertigo. All ten patients with BPPV who have had transection of the nerve are free of positional vertigo. This relief is immediate and lasting. PAN transection has been recommended only for those patients fitting the syndrome first decribed by Barany[2] and subsequently by others.[3-6] The objective findings include a mainly rotatory nystagmus directed toward the downmost ear which occurs after a short latency period and fatigues after a duration of 15 to 30 seconds.

TABLE 2. RESULTS OF POSTERIOR AMPULLARY NERVE TRANSECTION IN BENIGN PAROXYSMAL POSITIONAL VERTIGO (BPPV)

Patient	*Etiol. BPPV*	*Relief BPPV*	*Postop. H. L.*	*Postop. Eval.*
G. C.	Spont.	+	None	2.5 yr
J. O.	Spont.	+	Moderate	2.5 yr
A. L.	Sinus Surg.	+	None	21 mos
D. S.	Trauma	+	None	5 mos
M. L.	Spont.	+	None	3 mos

H. L. - Hearing loss.

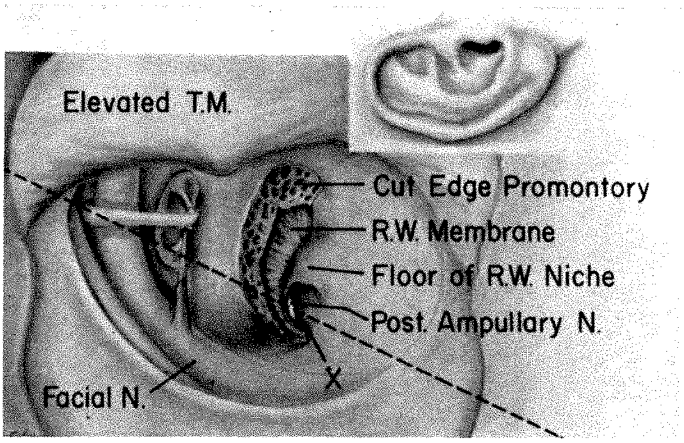

Fig. 2. Middle ear surgical approach to the posterior ampullary nerve utilizes the round window (RW) membrane as a landmark. Dotted line indicates the plane of section in Fig. 3.

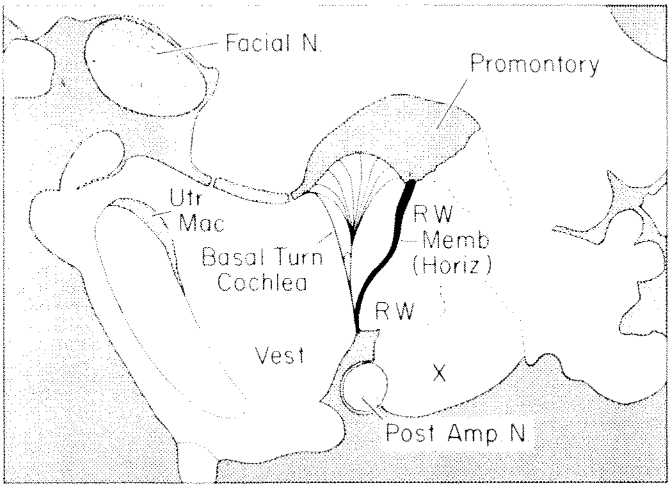

Fig. 3. Drawing of a vertical section through the singular canal. X - Excavation in floor of round window (RW) niche to expose posterior ampullary nerve. Dotted lines indicate bone removed by drill. Vest. - Vestibule. Utr. Mac. - Utricular macula.

The vertiginous experience and the objective findings are initiated by briskly placing the patient's head in either the right or the left ear down position. Furthermore, thorough otolaryngological and neurological evaluation should be performed to eliminate possible central nervous system pathology. Two patients in whom surgical exploration of the round window niche was carried out without transecting the PAN represent a control which establishes that the effective step in the procedure is the nerve transection. The BPPV persisted in these two patients. PAN transection via a middle fossa approach (Fig. 4) could be employed if the symptoms are severe.

This surgical treatment for BPPV indicates that the posterior semicircular canal sense organ is instrumental in the pathophysiology of the disorder. Previous indirect evidence of this statement consists of the finding of basophilic deposits embedded in the cupula of the posterior canal crista.[6,7] The theory of

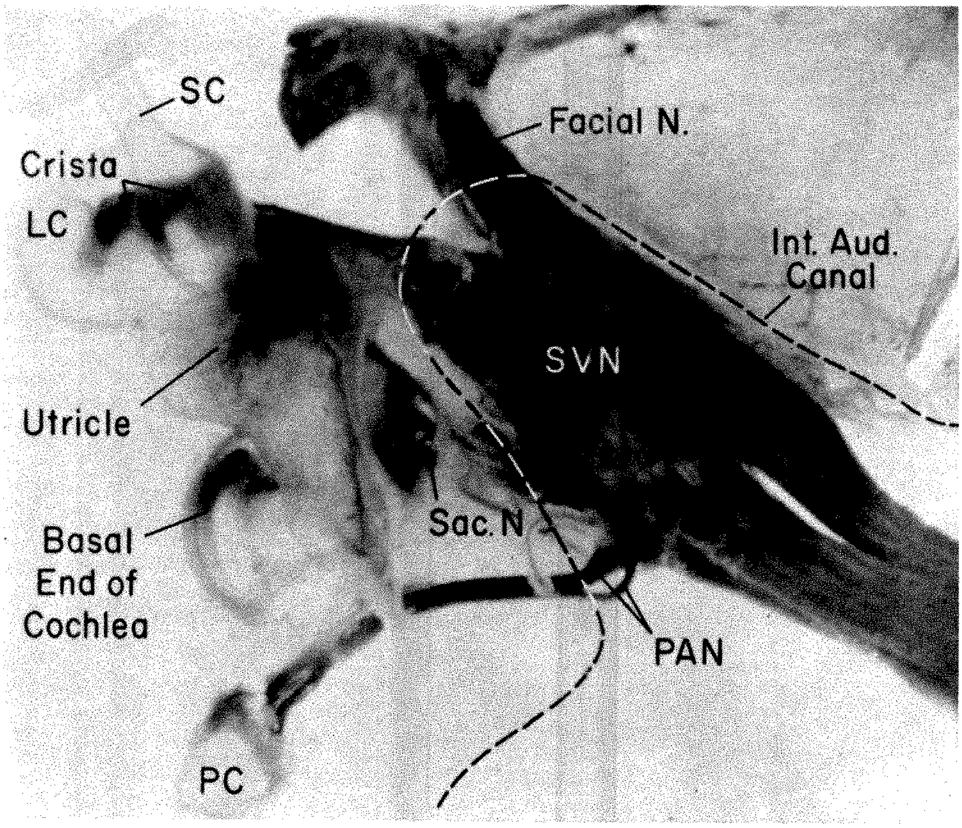

Fig. 4. Dissected human inner ear and nerve supply demonstrate the view from a middle fossa surgical approach to the internal auditory canal. Dotted line indicates the outline of the internal auditory canal. SVN - Superior vestibular nerve; PAN - Posterior ampullary nerve; Sac. N - Saccular nerve; SC - Superior semicircular canal; LC - Lateral semicircular canal; PC - Posterior semicircular canal.

cupulolithiasis is based upon this observation. Furthermore, anatomical[8] and physiological[9] evidence have demonstrated that the neural projection of the posterior canal crista is to the superior oblique and inferior rectus muscles, which are largely responsible for the primarily rotatory nystagmus with an inconsistent vertical component found in this order.

Although the posterior canal sense organ is important in the pathogenesis of BPPV, the entire mechanism by which the symptoms and findings are elicited has not been formulated. However, an enlarging body of clinical and laboratory findings suggests a working hypothesis of the pathophysiology.

The finding of basophilic deposits in the cupula of the posterior canal sense organ[6,7] may explain the initiation of cupular deflection upon assumption of a head position where the posterior canal crista is placed in a dependent position. The gravity sensitive cupula may respond to gravity, unlike a normal cupula during such a head positioning maneuver. Such a deflection would be temporary owing to the elasticity of the cupula which is also anchored to the roof of the ampulla. These properties return the cupula to a resting position following the very small deflection (fraction of degree) needed to cause excitation of vestibular hair cells. Thus, the physical properties of the sense organ and the gravity sensitive material deposited in the cupula could explain a limited period of rotatory nystagmus following a short latency period. The duration of nystagmus is fairly constant (Table 1) on the initial test maneuver. The fatigability of nystagmus is somehow related to the adaptability of the peripheral vestibular system.

The basophilic material in the cupula is likely a derivative of utricular otoliths loosened as a result of a degenerative labyrinthine process. This material resembles otoconia histologically and the utricular macula is the only possible source of degenerated otolith material in the pars superior of the labyrinth. Such a loss of otoliths suggests that utricular function may also be diminished because of a reduction in the shearing action which elicits stimulation of utricular macular hair cells. In some cases the utricular macula may be degenerated.[3] Stimulation of the utricular macula should also occur in the head down position used to elicit BPPV. Reduced utricular function may be important in this syndrome because of the demonstrated inhibitory effect of the utricle on semicircular canal function. This interdependence of the utricular and semicircular sense organs is based on: 1) the anatomical evidence of convergence of utricular and canal first order neurons in the medial vestibular nucleus[10] where excitatory vestibulo-ocular neurons[11] are located; and 2) the physiological demonstration that the posterior canal sense organ responds in an exaggerated fashion in animals where the utricular nerve has been selectively transected.[12-15]

It is well known that most cases of BPPV occur following a degenerative process in the labyrinth, such as from head trauma, ear surgery, aging, or vascular occlusion. The vast majority of such cases of paroxysmal positional vertigo, particularly those following head trauma, resolve spontaneously after a period of weeks or months. Only a small number of these cases are symptomatic for a year or more. A satisfactory explanation for this spontaneous remission of BPPV is lacking. It has been demonstrated by several morphologists that the composition of the otolithic membrane is such that the smaller otoliths are closer to the surface of the otolithic membrane while the large otoliths are located near the hair cell cilia. It is possible that the larger otoliths produce a more effective shearing action on the hair cell cilia because of gravitational pull. Following the various degenerative conditions mentioned above, small otoliths near the surface of the otolithic membrane are more likely to be dislodged while the large otoliths remain in contact with the hair cell cilia and therefore continue to respond to gravity. Utricular function may still be effective enough to control posterior semicircular canal activity. However, when large otoliths have been dislodged, the utricular macula may be rendered almost functionless. The syndrome of BPPV would continue because of unchecked posterior semicircular canal excitation following the assumption of the provocative head position.

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Ann Otol 87:1978

CRISTA NEGLECTA IN MAN

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SUMMARY — The prevalence, location, and size of the crista neglecta in man were investigated by examining the histological sections of 223 human temporal bones (137 cases). The relationship between the crista neglecta and the singular nerve was also described. The crista neglecta was observed in 17 cases, ranging in age from 15-week fetal life to 76 years. This structure was located on the wall of the anterolateral quadrant of the posterior canal ampulla, close to the cribriform area of the singular nerve in the area between the utriculoampullar duct and the intermediate portion of the posterior canal crista. The average width, length, and height of the crista neglecta were described. The crista neglecta had a mound-like shape and contained nerve fibers, transitional epithelium, sensory hair cells, and a cupula. The nerve fibers from the crista neglecta were joined to a small branch of the singular nerve at the cribriform area in 5 of 17 crista neglecta cases, and to the main trunk of the singular nerve in the remaining 12 cases.

The human crista neglecta is a small, vestibular sensory organ which is occasionally found in the posterior canal ampulla. Benjamins[1] (1913) identified this structure in a six-month fetus and reported it as the "fourth crista." This structure has been mentioned subsequently in only 10 cases.[1-5] The site of the crista neglecta has been variously described as being in the posterior canal ampulla,[2-4] in the entrance of the posterior canal ampulla,[5] and even in the inferior utricular sinus.[1] The nerve from the crista neglecta has been described as joining with the singular nerve,[2-5] but this relationship also has not been described in detail.

The purpose of this paper is to study the prevalence, exact location, and size of the crista neglecta in man. The relationship between the crista neglecta and the singular nerve is also described.

METHODS AND MATERIALS

A total of 223 human temporal bones (137 cases) were studied. Among them 45 were from 23 fetuses of 10, 12, and 15 weeks. The fetal temporal bones had been stored in 10% formalin and were decalcified, dehydrated, embedded in paraffin, and sectioned horizontally or sagittally at 30μ. The sections were stained alternately with Masson's trichrome or silver nitrate-gold chloride solution. The other 178 temporal bone specimens were from 114 individuals ranging in age from newborn to 102 years. Approximately two-thirds of these specimens were of infants or children. These specimens were fixed, decalcified, dehydrated, embedded in celloidin, and sectioned horizontally at 20μ. Every tenth section was stained

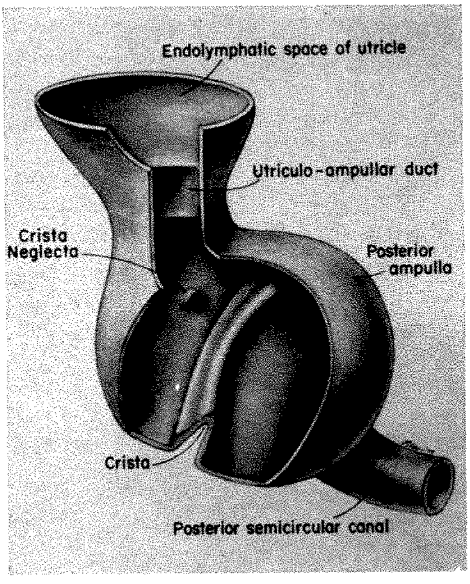

Fig. 1. This schematic drawing shows the usual appearance of the crista neglecta in the anterolateral quadrant of the posterior canal ampulla in man.

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TABLE 1. MEASUREMENTS OF THE CRISTA NEGLECTA

Case No.	*Age*	*Cause of Death*	*Width* A*	*Width* B**	*Length* A*	*Length* B**	*Height* A*	*Height* B**	*Distance from PCC*	*Height of Cupula*
1	15 wk fetus	Unknown	120	90	140	94	44	44	480	30
2	15 wk fetus	Unknown	210	118	230	118	60	60	420	25
3	15 wk fetus	Unknown	220	150	270	160	70	70	640	52
4	1 day	Hyaline membrane disease	210	170	200	180	60	60	550	M
5	9 day	Hydrocephalus	150	100	120	100	75	42	800	M
6	12 day	Respiratory disease	200	150	200	160	130	65	670	M
7	5 wk	Unknown	100	90	120	40	71	42	470	11
8	7 wk	A ganglionic megacolon	118	80	120	60	15	15	760	102
9	3 mo	Tracheoesophageal fistula	440	210	580	220	100	65	330	M
10	5 mo	Meningitis	580	360	500	440	40	40	520	200
11	1.2 yr	Hydrocephalus	170	110	180	80	85	49	660	10
12	1.5 yr	Osteopetrosis	120	80	100	50	50	50	370	M
13	12 yr	Diabetes mellitus	110	70	100	60	45	40	1000	100
14	17 yr	Kidney disease	240	160	220	180	60	59	680	M
15	50 yr	Coronary artery thrombosis	300	270	420	380	140	62	250	30
16	55 yr	Pneumonia	210	180	200	140	120	50	160	M
17	76 yr	Pulmonary embolism	200	110	180	140	30	25	440	10
		Average	217.5	146.9	228.2	153.0	70.3	49.3	541.2	

PCC - Posterior canal crista, M - Missing.
*A - Measurements of the crista neglecta in microns.
**B - Measurements of the sensory cell area of the crista neglecta in microns.

with H&E and mounted on a glass slide for light microscopic study. Additional sections were stained, as necessary, to confirm the presence of the crista neglecta.

TABLE 2. STATISTICS OF THE PRESENCE OF THE CRISTA NEGLECTA IN AGE

Age	*No. of Temporal Bones Studied*	*No. of Crista Neglecta Cases*	*Rate*
-0 (fetus)	45	3	6.6%
0-18 (infant to adolescent)	133	11	8.3%
18-102 (adult)	45	3	6.6%
Total	223	17	7.6%

RESULTS

The crista neglecta was observed in 17 temporal bones in 3 prenatal and 14 postnatal cases (Table 1). The prevalence of the crista neglecta in this study was 7.6%. There was, however, no statistically significant difference in the appearance of the crista neglecta with age (Table 2).

No particular relationships between the presence of the crista neglecta and severe, congenital anomalies or vestibular disturbances were observed. The cases did, however, include two hydrocephalic patients and one patient with a tracheoesophageal fistula of congenital origin. The clinical records were

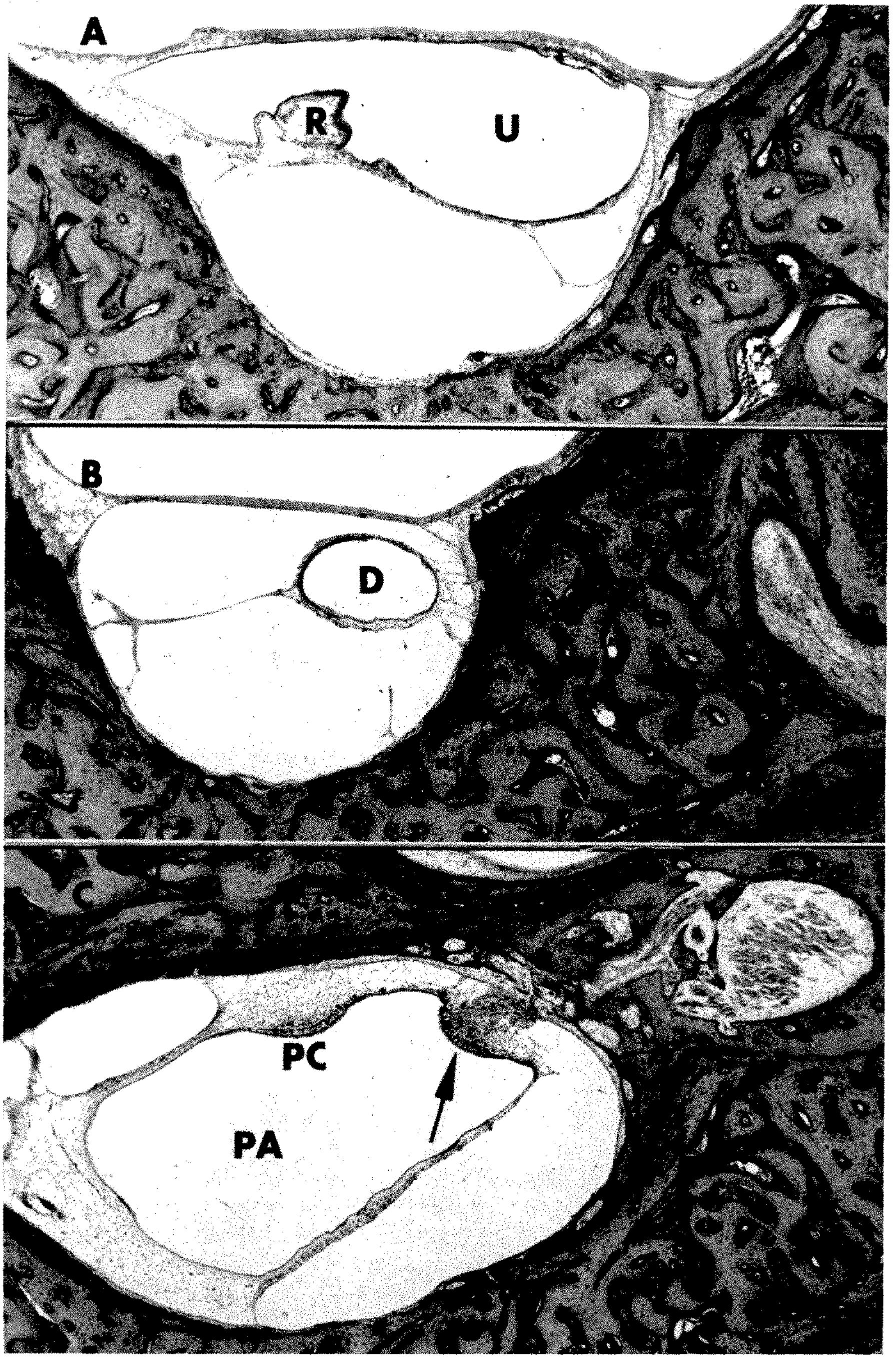

Fig. 2. (Case 9) Horizontal sections of the temporal bone of a 3-month-old infant demonstrate the anatomical relationships of the crista neglecta (arrow), to the posterior canal crista (PC), the posterior canal ampulla (PA), and the utriculoampullar duct (D). Note that the utricle and the posterior canal ampulla are separated by the utriculoampullar duct. R - Inferior utricular ridge. U - Utricular endolymphatic space. (H&E, X49)

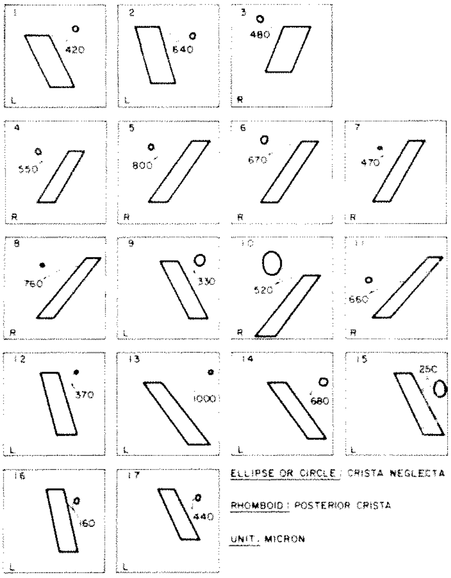

Fig. 3. A schematic drawing of the crista neglecta in a vertical plane view demonstrates its position relative to and distance from the posterior canal crista. The case number is indicated in the upper left corner. The right or left ear is indicated in the lower left of each frame. The number represents the distance in microns.

available in five of the postnatal cases, but did not describe any vestibular symptoms or disorders.

The crista neglecta was located on the wall of the anterolateral quadrant of the posterior canal ampulla close to the cribriform area of the singular nerve (Figs. 1, 2). None of the crista neglecta were found to be in the inferior utricular sinus. Figure 3 is a schematic drawing in the vertical plane showing the relative position of and distance from the crista neglecta to the true posterior canal crista in 17 cases. In two of those cases (Cases 11 and 15), the crista neglecta was located at the level of the intermediate portion of the posterior canal crista. In twelve cases (Cases 2, 4-10, 12, 14, 16, 17), the crista neglecta was located at the lateral edge of the posterior canal crista. In the three remaining cases (Cases 1, 3, 13), the crista neglecta was located slightly superior to the true crista of the posterior canal, close to the utriculo-ampullar duct. The average distance between the crista neglecta and the posterior crista

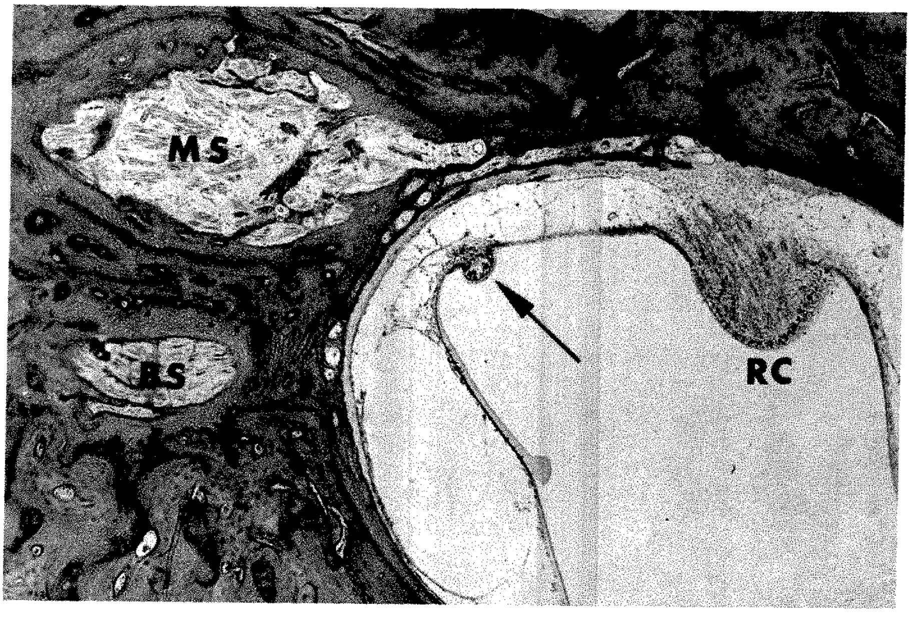

Fig. 4. (Case 7) The crista neglecta (arrow) in a 5-week-old infant shows the small branch of the singular nerve (BS) running separately from and posteriorly to the main trunk of the singular nerve (MS). The nerve from the crista neglecta joins to the small branch in this case. PC - Posterior canal crista. (H&E, X63)

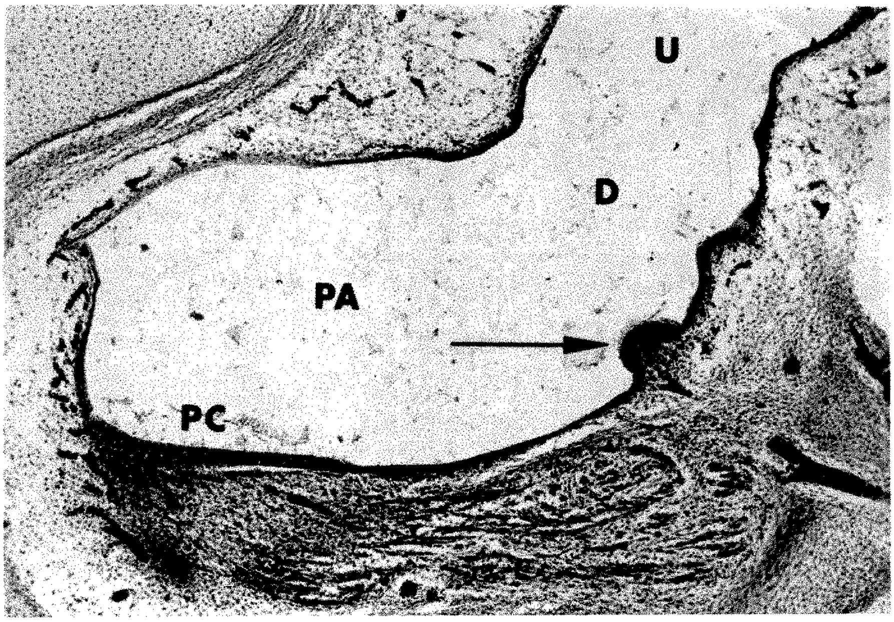

Fig. 5. (Case 3) Sagittal section of the crista neglecta (arrow) in a 15 week fetus demonstrates its location on the posterior canal ampulla. PC - Posterior canal crista. D - Utriculoampullar duct. PA - Posterior canal ampulla. U - Utricular endolymphatic space. (H&E, X76)

was 541.2μ in a horizontal section (maximum 1000, minimum 160).

The width, length, and height of the crista neglecta measured in the horizontal sections of the 17 cases are shown under Columns A in Table 1. The average width was 217.5μ (maximum 580, minimum 100); the average length was 228.2μ (maximum 580, minimum 100); and the average height was 70.3μ (maximum 140, minimum 15). The width, length, and height of the sensory cell area of the crista neglecta are shown under Columns B in Table 1. The average width was 146.9μ (maximum 360, minimum 70); the average length was 153.0μ (maximum 440, minimum 40); and the average height was 49.3μ (maximum 70, minimum 15). Thus, the crista neglecta was found to be extremely small and variable in size, with a wide range, and it was seen to be mound-like in shape (Fig. 3).

In all 17 cases, the crista neglecta possessed sensory hair cells, transitional epithelium, and nerve fibers to the singular nerve (Figs. 4, 5). In three prenatal cases, however, the sensory epithelium of both the crista neglecta and the true crista were still in primitive form. The cupula of the crista neglecta was identified in 10 of 17 cases (Fig. 6). In the remaining seven cases, the cupula of the true crista of the posterior canal was also absent, a condition found very often in human temporal bone specimens. It is interesting to note that besides those 17 cases mentioned above, in 11 additional postnatal temporal bones, only an atypical, epithelial mound without the sensory epithelial area for the crista neglecta was observed.

The branch of the singular nerve at the cribriform area was observed in 7 out of 17 crista neglecta cases. In all seven cases, the branch always innervated the posteromedial end of the posterior canal crista; however, in five of those seven cases, the nerve fibers of the branch innervated the crista neglecta, too. In the remaining 2 out of 7 cases, and in 10 cases lacking the branch, the main trunk of the singular nerve also innervated the crista neglecta; thus, in a total of 12 cases, the sin-

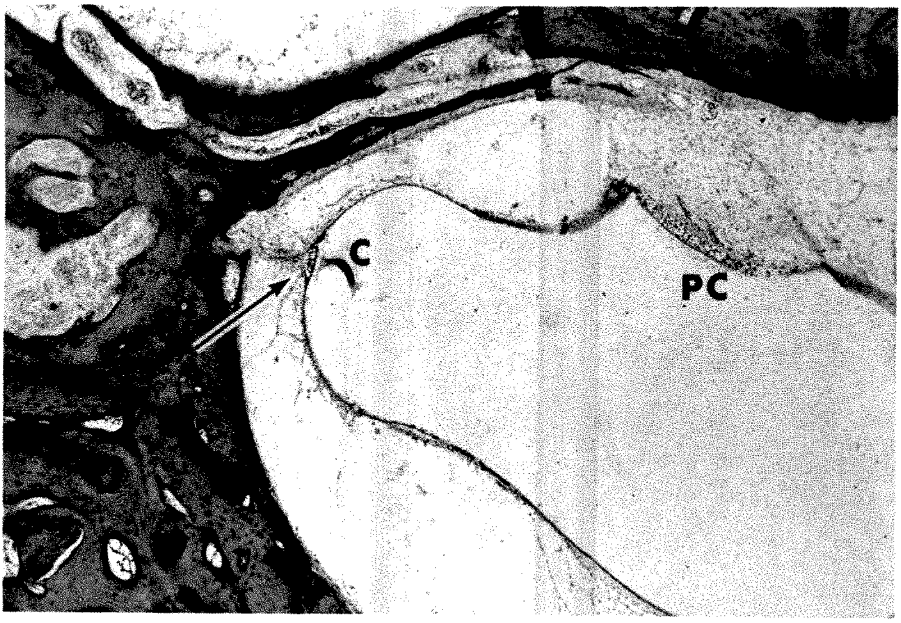

Fig. 6. (Case 8) The crista neglecta (arrow) in a 7-week-old infant demonstrates the cupula (C). PC - Posterior canal crista. (H&E, X72)

gular nerve also innervated the crista neglecta.

DISCUSSION

It is rare to find reports of the crista neglecta in human temporal bone studies. Since 1913, only ten cases have been reported.[1-5] The investigators of those cases variously designated this structure as the "fourth crista,"[1,2] the "accessory crista,"[3,4] and the "crista neglecta."[5]

The crista neglecta in man is not a "most unusual finding,"[4] since this structure was identified in 17 cases out of the 223 temporal bones examined in our study (7.6%). In 9 of the 17 cases (52%), the sensory epithelial area of the crista neglecta was observed only in one of every tenth stained section of the temporal bone in each case. Furthermore, in the remaining eight cases, the sensory epithelial area was observed only when every section was stained and studied. Therefore, it appears that if all temporal bone sections were examined as carefully as in this study, this structure would be identified more frequently.

The location of the crista neglecta has so far been briefly described. Benjamins[1] reported that this structure was located in the inferior utricular sinus, but demonstrated the crista neglecta in the posterior canal ampulla in one of his figures. Masuda,[2] Wolff,[3] and Altmann[4] described the crista neglecta as being inside the posterior canal ampulla, close to the true posterior canal crista. Montandon et al[5] described this structure as being in the area at "the entrance of the posterior canal ampulla into the posterior recess of the utricle."

The observation in the present study, that the crista neglecta is located in the lateral wall of the anterolateral quadrant of the posterior canal ampulla and between the utriculoampullar duct and the posterior canal crista, generally agrees with the descriptions in the previous reports.[1-5] Furthermore, with the present measurements of the distance between the crista neglecta and the true crista in our study, it appears that a detailed description of the location of this structure is now available.

Montandon et al[5] reported that the crista neglecta observed in two temporal bones was innervated by a branch of the singular nerve. In our cases, the branch at the cribriform area was observed in only 7 out of 17 crista neglecta cases (41.1%). Innervation of the crista neglecta by the branch was seen in 5 cases and innervation by the main trunk was seen in 12 of the 17 crista neglecta cases.

Montandon et al[5] hypothesized that in humans the crista neglecta normally is incorporated into the posterior canal crista. Of the 17 crista neglecta cases in our study, in 5 cases the branch of the singular nerve innervated both the crista neglecta and the posterior canal crista; in 12 cases the main singular nerve innervated both the true posterior canal crista and the crista neglecta. When the facts mentioned above are taken into consideration, it appears that the crista neglecta in man is an organ closely related anatomically and embryologically to the posterior canal crista.

We found the shape and size of the crista neglecta to be variable. Masuda[2] reported the dimensions as 330μ in length, 440μ in width, and 340μ in height. Wolff[3] reported the crista neglecta as being mushroom-shaped and measured the width as 160μ, and the height as 160μ. Our data indicates that the shape was mound-like, and that it is about 217μ in width, 228μ in length, and 70μ in height.

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Reprints — Eugene N. Myers, MD, University of Pittsburgh School of Medicine, Eye and Ear Hospital, Pittsburgh, PA 15213.

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BIOLOGICAL EFFECTS OF NOISE

The International Commission on Biological Effects of Noise announces the Third International Congress on Noise as a Public Health Problem: Biological and Behavioral Effects, September 25-29, 1978 in Freiburg, Federal Republic of Germany (West Germany). Inquiries should be addressed to: International Commission on Biological Effects of Noise, Institut für Arbeits- und Sozialmedizin, Universitätsklinikum, Johannes Gutenberg Universität, Obere Zahlbacher Strasse 67, D-6500 Mainz, Federal Republic of Germany.

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NEURILEMOMA OF THE JUGULAR FORAMEN
TRANSMASTOID REMOVAL

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SUMMARY — The authors present two cases in which the palsies of the IX, X, XI and XII nerves heralded the presence of a neurilemoma within the jugular foramen. Temporal bone polytomography, retrograde jugular venography, and pantopaque posterior fossa myelography allowed the nature and extent of the tumor to be predicted accurately prior to the operation. The tumors were completely removed using a transmastoid-extended facial recess approach without labyrinthectomy, supplemented in one case by exploration of the upper cervical portion of the internal jugular vein. This technique has avoided the complications which attend removal by way of the posterior fossa. We feel that transmastoid removal merits more extensive clinical trial.

At least 12 different diseases can evoke the jugular foramen syndrome. Despite this, multiple palsies of the lower four cranial nerves are rarities. How, then, does one progress expeditiously to a diagnosis, establish the extent of the lesion and determine operability? This paper reports the diagnostic maneuvers which allow one to judge the cause and extent of jugular foramen lesions and describes a new method of removal for one of the less common causes of the jugular foramen syndrome, a neurilemoma.

LITERATURE REVIEW

Tumors derived from the structures within or adjacent to the jugular foramen[1] include meningioma, chordoma, neurilemoma, glomus tumor, chondroma, carcinoma of the tympanic cavity, epipharyngeal carcinoma, epidermoid cysts, neurofibroma,[2,3] sympaticoblastoma,[3] myxofibrosarcoma[2] and aneurysm of the internal carotid artery. Glomus tumors occur most commonly. Neurilemomas are rare. Whereas individual reports of glomus tumors comprise as many as 316 cases,[1] only 23 neurilemomas of the jugular foramen exist in the world literature.[2-8]

The surgical attack, when attempted, was suboccipital in all but one case: Mountjoy et al[8] removed a neurilemoma of the IX nerve through a translabyrinthine approach.

Neurilemomas occur more often in the intracranial or extracranial portions of the IX, X, XI, and XII cranial nerves than in the foramen itself.[2]

Intracranial neurilemomas[2,5,9] typically present multiple cranial nerve palsies; they may be confused with acoustic neuromas,[6,7] which also can invade the jugular foramen. An intracranial neurilemoma of one of the four lower cranial nerves can infiltrate the jugular foramen without producing a jugular foramen syndrome. Such predominantly intracranial tumors have only been approached via suboccipital craniectomy heretofore.

Predominantly extracranial neurilemomas can cause a jugular foramen syndrome, but most exhibit only a single nerve palsy and a mass in the neck or lateral pharyngeal wall.[10] Earlier authors[2] have recommended exposing such tumors through the neck, although one[11] partially removed a dumbbell intracranial-extracranial hypoglossal nerve neuroma through the neck and posterior fossa sequentially.

Metastatic carcinoma may produce a jugular foramen syndrome by invading

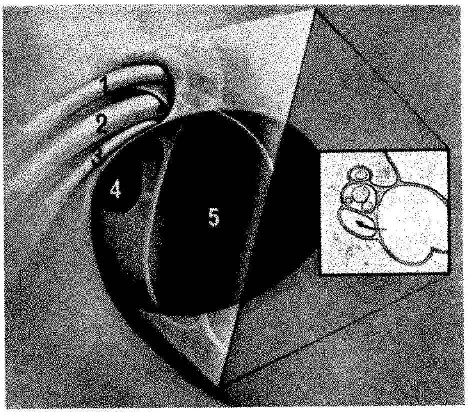

Fig. 1. Relationships of the cranial nerves within the jugular foramen. 1) IX cranial nerve; 2) X cranial nerve; 3) XI cranial nerve; 4) inferior petrosal sinus; and 5) jugular bulb.

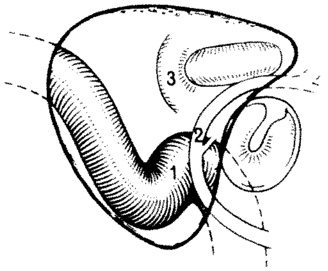

Fig. 2. Surgical relationships of the jugular bulb to overlying structures. 1) jugular bulb; 2) vertical segment of facial nerve; and 3) posterior semicircular canal.

lymph nodes adjacent to the foramen and infiltrating the exiting lower four cranial nerves.[2,4]

The jugular bulb may enlarge as an anatomic variant or in response to an intracranial aneurysm or anteriovenous malformation.[2] In such instances the pars venosa retains smooth, well-outlined margins, and the pars nervosa remains normal in shape and dimensions. Cranial nerve palsies are absent.

ANATOMY OF THE JUGULAR FORAMEN

Authors disagree on the exact location of the IX, X, and XI nerves within the jugular foramen. Some maintain that the X and XI nerves are located in the pars venosa of the foramen.[8,12] Others indicate that all three pass in the pars nervosa.[3,7] Both points of view may be correct.

At the posterior fossa entrance to the jugular foramen the anteriomedial pars nervosa is separated from the posterolateral pars venosa by the intrajugular process of bone supplemented by a fascial ligament. On occasion a complete septum of bone separates the two compartments.[4] The pars nervosa transmits the IX cranial nerve, the vena canaliculi cochleae and the inferior petrosal sinus. Both these veins cross the pars nervosa to reach the jugular bulb. The pars venosa contains the jugular bulb and the X and XI cranial nerves.[13] A tripartite division of the inlet may also occur.[12]

As the IX nerve passes deeper into the jugular foramen it retains a separate dural sheath and lies in a deep groove which in 25% of cases is a separate bony canal. Just posteriorly the X and XI nerves, enveloped by a common dural sheath, lie in the same groove posteromedial to the jugular bulb itself. Figure 1 illustrates these relationships.

The hypoglossal canal converges with the internal jugular vein at the outlet of the jugular foramen and terminates at or a few millimeters away from the posteromedial margin of the foramen. Emerging from the canal, the XII nerve lies on a deeper plane than the internal jugular vein and the bundle containing the IX, X, and XI nerves.

SURGICAL APPROACH TO THE JUGULAR BULB

A cortical mastoidectomy is first performed, exposing the posterior bony semicircular canal, the descending portion of the facial nerve, and the sigmoid sinus. The sigmoid sinus is packed off with oxidized regenerated cellulose (Surgicel®). The internal jugular vein is ligated through an extension of the mastoid incision into the upper neck. After further exposing the facial nerve through the facial recess, one may mobilize it from the canal and retract it anteriorly as necessary.

Figure 2 illustrates the surgical anatomy. One can usually secure access to the anterior half of the jugular bulb through the posterior facial recess with-

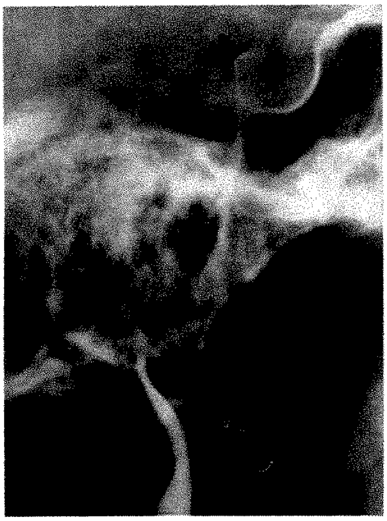

Fig. 3. (Case 1) Retrograde jugular venogram. Arrow indicates area of extrinsic compression.

out disturbing the ear drum or ossicular chain. However, the facial nerve must be rotated anteriorly to expose the entire bulb from behind.

One must approach the jugular bulb with a diamond drill, using continuous irrigation and the operating microscope. The diamond drill can remove bone from the wall of the vessel without disrupting it if no pressure is applied. Bipolar cautery will control bleeding from smaller vessels, but only packing controls hemorrhage from the lacerated jugular bulb itself.

In neurogenous tumors of the jugular bulb, hemorrhage is less troublesome than in glomus tumors. However, upon removal of the deep portion of the tumor, the inferior petrosal sinus may bleed at its point of entry into the dome of the bulb. Preparations should be made to pack it immediately with oxidized regenerated cellulose and to administer blood.

One usually cannot separate the individual cranial nerves from a neurogenous tumor mass of the bulb. Therefore, the nerves should be sectioned as they enter the mass from below. The nerves can be cut proximal to the tumor mass after the tumor mass and any involved dura have been resected.

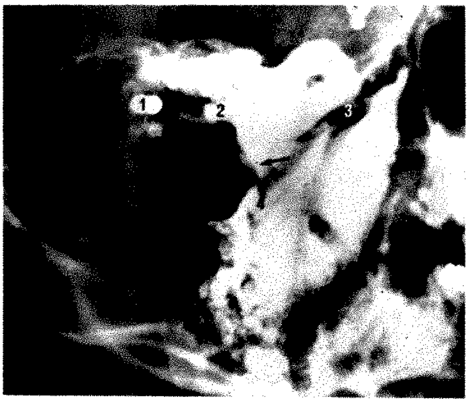

Fig. 4. (Case 1) Posterior fossa myelogram. Arrow indicates mass within posterior fossa. 1) steel marker in right ear canal; 2) right internal auditory canal; 3) basilar artery; 4) right vertebral artery.

Deficiencies in the dura are filled with pieces of autogenous fat or muscle large enough to obliterate the volume of the mastoid cavity as well.

If the neurogenous tumor extends into the neck, one may expose it after detaching the upper end of the sternomastoid muscle, removing the mastoid tip, resecting the posterior belly of the digastric muscle and exposing the facial nerve from the stylomastoid foramen to its primary division within the parotid gland. Gardner[14] has described and illustrated this approach to the carotid sheath structures at the base of the skull.

CASE REPORTS

Case 1. The patient, a 43-year-old woman, complained of choking on liquids and hoarseness for four months duration. Her right shoulder had felt sore for six months. Physical examination disclosed palsies of the right IX, X, XI and XII cranial nerves. Auditory and vestibular function was normal, as was ear drum appearance.

Petrous pyramid polytomograms showed an enlarged right jugular foramen with some erosion medially and superiorly. A retrograde jugular venogram (Fig. 3) demonstrated extrinsic blockage of the vein at the jugular bulb. Posterior fossa myelogram (Fig. 4) demonstrated a defect measuring 2.2 cm in greatest diameter projecting from the region of the bulb into the posterior fossa just below the internal auditory canal, which filled well. A right carotid arteriogram opacified fine vessels within the jugular bulb which extended a short distance down the internal jugular vein.

A preoperative diagnosis of neurogenous tumor of the jugular foramen was made. Mastoidectomy through a postauricular approach and exploration of the posterior half of the middle ear by way of the extended facial recess confirmed that the tumor did not invade these areas. Bone was removed beneath the mastoid segment of the facial nerve and from the sigmoid sinus and jugular bulb.

The tumor, once exposed, appeared to be extradural, but extended into the petrous apex inferior to the internal auditory canal almost to the odontoid process. The jugular bulb, although compressed, was not infiltrated. The IX, X, and XI nerves disappeared into the mass. After part of the tumor had been removed, the vein was packed with Surgicel® above and below the tumor. The tumor was then completely excised, along with a small area of involved dura. A free muscle graft filled the dural defect. She lost 700 cc of blood. We could not determine from which of the involved nerves the tumor originated.

Seven weeks after surgery we observed thickening of the right tympanic membrane and reduced tympanic membrane compliance, which suggested that there might be CSF in the middle ear. These findings had cleared at her six-month checkup. Although the tumor has not recurred, she shows no return of function of the involved nerves two years after surgery. Hearing is now normal in the involved ear.

Case 2. This 23-year-old woman consulted her physician because of fullness in the left ear, slightly decreased hearing and tinnitus two years before we examined her.

Diagnostic left myringotomy six months later had revealed a mass in the hypotympanum, which proved to be a neurilemoma on biopsy. She had no cranial nerve deficit at that time, and no treatment was recommended. She had developed a weak voice, difficulty manipulating her tongue, and left shoulder discomfort when we examined her 18 months later.

A firm, grayish-white mass distended the inferior half of the left tympanic membrane. She had a 30 dB conductive type hearing loss in the left ear, normal discrimination, and palsies of the left IX, X, XI and XII cranial nerves.

Petrous pyramid x-rays showed a 3 cm defect in the region of the left jugular foramen and destruction of the floor of the left internal auditory canal. A posterior fossa myelogram demonstrated a mass projecting from the jugular foramen approximately 1 cm into the posterior fossa which blocked the entrance of the internal auditory canal. An arteriogram showed a moderate amount of abnormal vascularity in the mass. The internal carotid artery was displaced anteriorly and slightly compressed in its anteroposterior diameter. Jugular venography showed that tumor occluded the jugular bulb and compressed the vein extrinsically as far as the inferior border of C-1. No dye entered the inferior petrosal sinus or the sigmoid sinus.

The lesion was exposed by a transmastoid extended facial recess approach. The neurilemoma involved the hypotympanum and retrofacial cells. The facial nerve was extracted from the facial canal from the stylomastoid foramen to the lateral semicircular canal and was rotated forward to allow better exposure of the tumor. The internal jugular vein was ligated at C-2 level through a contiguous neck incision. The tumor displaced the internal carotid artery anteriorly and inward. A Surgicel® pack controlled the bleeding from the carotid area during tumor removal. The tumor invaded the basal turn of the cochlea, exposed the dura of the internal auditory canal and completely destroyed the nerves traversing the jugular foramen. Some of the dura overlying the jugular bulb was removed along with the tumor. Filling the mastoid cavity with Surgicel® controlled the bleeding and the spinal fluid flow. No tissue graft was used. Blood loss was 2500 cc.

A left facial palsy, noted at the end of surgery, cleared within two months. Continuous cerebrospinal fluid leakage necessitated reopening the wound, removing the Surgicel® and inserting a free muscle graft three days postoperatively. Hearing was lost in the left ear, and palsies of the lower four cranial nerves on the left persisted, but we found no tumor recurrence two years later.

DISCUSSION

One must conduct a complete radiologic evaluation to determine the exact location and extension of any tumor of the jugular foramen. An extension of tumor into the posterior fossa, petrous apex and neck is possible. Polytomography will indicate the extent of bone invasion. A pantopaque study of the posterior fossa best reveals intracranial extension. Retrograde jugular venography will differentiate intraluminal invasion of the jugular bulb from extrinsic compression and will demonstrate whether the tumor projects distal to the outlet of the jugular foramen.

Glomus jugulare tumors produce a distinctive multilobular filling defect within the jugular bulb and internal jugular vein. Neurilemomas produce extrinsic compression of the bulb and occasionally the adjacent internal jugular vein. Invasion of the posterior fossa or carotid artery compression may prevent surgical attack upon a glomus tumor, but need not deter one from operating a neurilemoma. Some neurilemomas do not show "tumor blush" on arteriography. Others will, as will most meningiomas and all glomus jugulare tumors. Therefore, the absence of arterial blush within the tumor eliminates the possibility of a glomus tumor. Arteriography will also identify an intracranial aneurysm or arteriovenous fistula.

Twelfth nerve palsy suggests tumor invasion either of the hypoglossal canal or of the hypoglossal nerve distal to the canal. In such a case one must explore the area of the neck immediately distal to the outlet of the jugular foramen.

The majority of tumors recognized to date have been removed by suboccipital approach. However, a substantial proportion of the individuals who underwent posterior fossa exploration suffered residual cerebellar ataxia and additional cranial nerve palsies. The transmastoid-extended facial recess approach, developed for the removal of glomus tumors,[14-16] offers good surgical access to the jugular foramen and allows a tumor extending intracranially to be removed without damage to the cerebellum. The exploration may proceed into the neck for ligation of the internal jugular vein and removal of any cervical tumor extension. One can excise portions of the tumor invading the middle ear and hypotympanic air cells through the extended facial recess approach without damaging the tympanic membrane or ossicular chain. The auditory and vestibular labyrinth may be spared except when invaded by tumor, or when one needs wide access to the posterior fossa for removal of a predominantly intracranial tumor.

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FLEXIBLE BRONCHOSCOPY IN NONVISUALIZED CARCINOMA OF THE LUNG

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SUMMARY — Of 1,000 consecutive patients undergoing fiberoptic bronchoscopy, 331 eventually were proven to have primary lung cancer. Of the 331 carcinomas, 253 were beyond the visual range of the flexible bronchoscope. However, under fluoroscopic guidance, the diagnosis of carcinoma was established in 194 (76.7%) of these nonvisualized tumors. Cytologic analysis of brush specimens was more often positive for malignancy than specimens obtained by forceps biopsy. An expert cytologist and experienced bronchoscopy team are essential for a high percentage of reliable positive diagnoses in bronchogenic carcinoma.

Most pulmonary carcinomas begin in a segmental or subsegmental bronchus presenting radiographically as areas of atelectasis or peripheral nodules. Attempts have been made to establish accurate radiographic diagnostic criteria for carcinoma including configuration of shadows, presence of calcification and doubling time,[1] as well as clinical criteria such as evidence of airway obstruction, metastases and metabolic syndromes secondary to carcinoma.[2]

Preoperative confirmation of carcinoma is usually attempted by sputum cytology[3] and examination of biopsy material obtained by bronchoscopy, mediastinoscopy or from tissue from distant metastases.[4] However, patients with peripheral lung tumors frequently fail to produce sputum and biopsy through the conventional rigid bronchoscope is limited to major bronchi and inferior segmental bronchi.[5]

With the introduction of the fiberoptic bronchoscope by Ikeda,[6] visualization of the tracheobronchial tree has been increased by more than 50%, improving the rate of positive pathologic and cytologic diagnosis. Yet, many tumors are located in subsegmental bronchi, beyond the visual range of even this resourceful instrument. These nonvisualized lesions spurred the use of the ancillary flexible brush and forceps under fluoroscopic control, resulting in recent reports of up to 90% accuracy in diagnosis of pulmonary carcinoma.[7,8]

It is the purpose of this communication to report the results of flexible brush and forceps biopsies via the fiberoptic bronchoscope under fluoroscopic control in 331 patients with proven carcinoma of the lung, with particular emphasis on 253 patients in whom the neoplasm was not seen endoscopically.

METHODS AND MATERIALS

From March 1974 to February 1977, 1,000 patients were subjected to fiberoptic bronchoscopy at the Mount Sinai Medical Center, New York City, for a variety of indications including hemoptysis, cough, opportunistic pulmonary infections, diffuse pulmonary diseases, and various radiographic abnormalities such as segmental and lobar atelectasis, persisting consolidation and patchy or nodular peripheral densities. Most patients with tumors clinically thought to originate in major or lobar bronchi were referred to the Otolaryngological and Cardiothoracic Surgical Services for rigid bronchoscopy. Thus, the patients who are the subject of this report and underwent flexibile bronchoscopy by the Pulmonary Division of the Department of Medicine manifest an unusually high percentage of "peripheral" carcinoma of the lung.

From the Departments of Medicine and Pathology, Mount Sinai School of Medicine, New York. This work was supported by the Henry and Catherine Gaisman Foundation.

TABLE 1. POSITIVE DIAGNOSIS BY FIBEROPTIC BRONCHOSCOPY IN PATIENTS WITH PRIMARY CARCINOMA OF THE LUNG (N = 331)

	No.	*Brush*	*Forceps Biopsy*	*Combined Brush and Forceps*
Visualized	78	70 (89.7%)	52 (66.7%)	74 (94.9%)
Nonvisualized	253	181 (71.5%)	121 (47.8%)	194 (76.7%)
Total	33	251 (76%)	173 (52%)	268 (81%)

The Olympus BF-5B2 fiberoptic bronchoscope was employed according to the method previously reported.[9] In all patients secretions and saline washings were aspirated and brush biopsies performed for cytologic and bacteriologic analysis. Except where contraindicated because of active bleeding, forceps biopsies were also performed. The cytologic specimens obtained by brushing were immediately smeared on clean glass slides and sprayed with standard fixative. The forceps biopsy specimens were immersed in 10% formalin.

RESULTS

Of the 1,000 patients, 331 proved to have primary carcinoma of the lung. The remaining 669 had a variety of other pulmonary diseases. Only 78 of the 331 carcinomas were visible via the flexible bronchoscope and 253 were beyond the optical range of this instrument. One hundred and eighty-one of the 253 (71.5%) had positive brush and/or aspiration cytology for malignant cells (Table 1). One hundred and twenty-one (47.8%) had positive forceps biopsies. There were 59 patients with positive brush biopsies and negative forceps biopsies, while there were 14 with positive forceps biopsies and negative brush biopsies. Combining both brush and forceps biopsies, the diagnosis of carcinoma in nonvisualized tumors was established in 194 of the 253 (76.7%) patients. It is of interest that even in the 78 patients with visualized neoplasms, positive brush biopsies exceeded that of forceps biopsies; 89.7% positive by brush and 66.7% positive by forceps. Overall, a positive diagnosis of carcinoma was established in 81% of the 331 patients with carcinoma.

A significant finding was the improvement of diagnostic accuracy which prevailed after the first year of experience with the procedure. Whereas the diagnosis of primary pulmonary malignancy was established in 64.3% of 42 patients with nonvisualized carcinoma undergoing bronchoscopy during the first year of the study, thereafter the diagnosis was obtained in 84% of similar patients.

In the 669 patients without carcinoma, there was one false positive diagnosis of carcinoma by cytology. This patient had acute leukemia, was receiving chemotherapy and had bronchoscopy to determine the etiology of an opportunistic pneumonia. In one patient with proven carcinoma, forceps biopsy revealed only noncaseating epithelioid granulomas, but cytologic analysis of the brush biopsy specimen yielded the correct diagnosis of carcinoma.

DISCUSSION

Prior to fiberoptic bronchoscopy, the diagnosis of carcinoma rested on a compatible clinical and/or radiographic presentation confirmed by sputum cytology, rigid endoscopic or surgical biopsy. In carcinoma, atelectasis, hilar lymph node enlargement, pleural effusion and peripheral nodules are the predominant intrathoracic radiographic abnormalities. Enlargement or progression of radiographic densities, with time, is of immeasurable aid to the diagnosis. Yet, none of these roentgen patterns is specific for primary pulmonary carcinoma and errors in over- and underdiagnosis were common. Peripheral noncalcified nodules presented an especially difficult diagnostic problem. Steele has noted that only 50% of noncalcified lesions in males over the age of 50 prove to be carcinomas after resection.[10]

Confirmation by positive sputum cytology in lung cancer has varied widely about the world. In a comprehensive review in 1966, Davies reported that positive sputum cytology ranged from 23.7 to 79%.[11] Oswald noted only 48% positive sputum cytology in 2,545 patients, with the rate of positivity increasing to 85% when at least four sputum specimens were examined.[12]

Rigid bronchoscopy, with its relatively limited field of vision, yields positive biopsies in approximately 50% of all patients with carcinoma of the lung.[5] Using a flexible brush and the rigid bronchoscope, Fennessy was able to obtain a positive diagnosis in 69% of patients.[13] The yield of other biopsy procedures such as mediastinoscopy, peripheral lymph node biopsy, pleural biopsy, liver biopsy and bone marrow biopsy varies with the presence of metastases. These procedures have their greatest use in the determination of resectability.

The flexible fiberoptic bronchoscope affords an opportunity to histologically confirm the presence of carcinoma in a high percentage of patients. Through this instrument one may directly view and remove specimens from all third and fourth order bronchi, 86% of fifth order bronchi, and 55% of sixth order bronchi.[14] Employing the flexible forceps, biopsy specimens may be obtained from most of the segmental and subsegmental bronchi. However, the 2 mm forceps must be opened to a 4 mm span between its "jaws" in order to obtain an adequate biopsy specimen, thus impeding its approach to many peripheral lesions. The 2 mm brush may be introduced to the outermost recesses of the peripheral airways, reaching almost to the terminal bronchioles. Therefore, under fluoroscopic control, brush biopsy and cytologic analysis of specimens afford the best chance of establishing the diagnosis of nonvisualized peripheral carcinoma: 71.5% versus 47.8% by forceps biopsy in the current study. Utilizing both brush and forceps biopsies the diagnosis of nonvisualized carcinomas of the lung should be possible in at least three fourths of all suspect patients.[15]

It is noteworthy that after the first year of experience with the technique of fiberoptic bronchoscopy and ancillary brushing and forceps biopsy under fluoroscopic guidance, the rate of positive specimens obtained increased to 84.8%. This high percentage of correct diagnoses could be attributed to both the increased experience of the bronchoscopic team and the simultaneous acquisition of the services of an expert cytologist.

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SECOND INTERNATIONAL SYMPOSIUM ON OTITIS MEDIA WITH EFFUSION

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VII. Outcome (Sequelae).

Please send a one-page abstract by September 1, 1978 to: David J. Lim, MD, Department of Otolaryngology, Ohio State University Hospitals, 456 Clinic Drive, Columbus, OH 43210.

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STUDY OF SPASTIC DYSPHONIA USING VIDEOFIBEROPTIC LARYNGOSCOPY

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SUMMARY — Spastic dysphonia is a speech disorder, characterized by a "strangled voice quality," irregularly occurring phonatory arrests, and a jerky pattern of speech. This is often extremely disruptive to the patient's ability to communicate. Two cases are presented in which a new technique, videofiberoptic laryngoscopy, was employed in the study of these patients. The characteristic laryngeal behavior of this disorder is documented and recorded, particularly noting the increase in supraglottic activity and how different vocal maneuvers alter this activity.

Spastic dysphonia is a speech disorder which occurs relatively infrequently, but which can severely disrupt vocal communication and be extremely disturbing to the patient. Perceptually, a number of vocal features are characteristic of spastic dysphonia.[1-5] It may be characterized by reduced vocal intensity, an intermittent strangled vocal quality and irregularly occurring phonatory arrests which result in a jerky pattern of speech. Vocal pitch is usually inappropriately low but a choked, high-pitched strained sound may also be heard. Expressive functions of speech, such as speaking to oneself, whispering, and singing, and reflex phonatory actions (laughing, coughing) are affected to a lesser degree.

Aronson[5] designates two specific types of spastic dysphonia, the more common of which is the adductor type, characterized by laryngospasms during glottal closure. The second is an abductor type consisting of abrupt widening of the glottis which produces a brief instance of aphonia or breathy dysphonia. In addition to these two types, Cooper[3] describes an incipient stage of spastic dysphonia which is a less severe form and which preceded the more commonly depicted spastic dysphonia in nearly all of his cases.

Structurally, the larynx appears to be normal. Examination via indirect laryngoscopy reveals either normal true cord activity or midline approximation of the false vocal folds. Extreme tension of the chest and abdominal muscles with jerky respiration may also be evident along with engorgement of neck veins, flushing of the face, and eye blinking.[3,5]

There have been two divergent schools of thought regarding the etiology of the disorder. Originally, it was considered a psychogenic voice disorder, classified by some as a conversion reaction. The preponderance of literature supports the notion that spastic dysphonia is psychogenically based.[4,6,7] Heaver[6] described in detail the psychiatric aspects of the disorder.

The second theory purports a neurological basis as an underlying cause. Robe et al[8] presented evidence in which ten patients with spastic dysphonia all exhibited some extrapyramidal abnormalities. Aronson et al[9,10] provided evidence suggestive of a neurological basis in some of the patients they studied. Aronson[5] pointed out that in contrast to vocal pathologies of a conversion

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(psychogenic) nature, in spastic dysphonia one finds 1) an equal sex ratio, 2) resistance to voice therapy, and 3) laryngospasm.

Cooper[3] has proposed a third etiology, long-term vocal misuse with psychological or physical trauma often being the catalysts. His treatment accordingly consists of intensive vocal therapy and vocal psychotherapy.

More definitive information regarding structural movements might be useful as a means of better understanding both the pathological processes and treatment for spastic dysphonia. Presently, most information is based on indirect laryngoscopy or operating room observations empirically derived. The disease remains poorly understood despite its original description by Traube in 1871.[7] There has been little documentation or objective analyses of laryngeal function of this disorder. A recent effort at documenting activity along the vocal tract in patients with spastic dysphonia was reported by McCall et al.[11] Using videofluoroscopy, these investigators noted some atypical movement patterns of both laryngeal and pharyngeal structures.

Sawashima and Hirose[12] designed a flexible fiberoptic laryngoscopy which allows direct visualization of the larynx during function. With this technique, one oberves the laryngeal condition during connected discourse with relatively little disturbance to the movements of the other structures of speech. Brewer and McCall[13] have also utilized this technique, illustrating how the flexible fiberoptic laryngoscope aids the treatment planning of voice therapy and documents improvements in laryngeal functioning for phonation with such therapy.

No reports have appeared in which laryngeal functioning has been studied in patients with spastic dysphonia using videofiberoptic laryngoscopy. Two cases are presented herein in which this instrumentation was employed to study laryngeal activity in such patients. Sound recordings were obtained simultaneously with the videotape recordings to allow observation of laryngeal movement associated with the characteristics of the voice.

METHODS AND MATERIALS

Two patients with spastic dysphonia underwent videolaryngoscopy using the Olympus flexible fiberoptic bronchoscope (FFB), (BF type 5B2).

Each subject was first injected with 0.2 mg of atropine sulfate to reduce secretions. The nose and mouth were then anesthetized with cocaine flakes (less than 100 mg) in the nasal cavity and 4% Xylocaine® sprayed into the oral cavity and oropharynx.

The FFB was then introduced into one nostril and passed down through the naso- and hypopharynx until the epiglottis was identified. The position of the tip of the scope was varied from the superior border of the epiglottis to a point just above the vocal cords, depending on the tolerance of the patient and the maneuvers to be observed. The viewing lens of the FFB was then attached to the video recording and monitoring apparatus (Concord PCC 49 color television camera, Electrohome 63.5 cm color television monitor; Panasonic NV 3130 videotape recorder). With the larynx and vocal cords visible, the patient was asked to perform various vocal and nonvocal maneuvers. Readjustment of the position of the tip of the FFB was often necessary in an effort to maintain adequate visualization.

After the procedure was completed, the authors reviewed the videotapes. The tape could be replayed in regular or slow motion, or could be stopped so as to freeze the image of the structures. Each replay mode was utilized, permitting careful evaluation of laryngeal activity. A tape of a normal subject who had also been examined with the videofiberoptic laryngoscope was used as a basis of comparison.

CASE REPORTS

Case 1

A 46-year-old female in December 1973 had an otolaryngologic examination for a complaint of nasal congestion. During the examination, a speech problem was noted. She was told that she had poor habits of speech and that she could correct her speech herself. She attempted to do so but her voice deteriorated further. The patient indicated that vocal fatigue, effort in talking and a feeling of tension in her throat became noticeably pronounced. Examination in October 1975 by another otolaryngologist revealed normal vocal cords. One month of voice therapy following this examination produced temporary improvement of the voice.

Physical Examination. The patient was an anxious, overweight female who had a normal ENT and general physical examination.

Speech Evaluation. The patient presented an inappropriately low vocal pitch and strained, jerky phonation. Some speech sounds were missing during conversation. This occurred sporadically throughout an utterance and was not related to any particular sounds. The episodes of missing speech sounds seemed to be associated with an abrupt cessation of phonation and contributed to the jerkiness of the patient's speech. Vocal fry was also evident along with mild, intermittent grunting. Respiration during voice production was shallow and tense. There were a few instances of vocal improvement with clinical stimulation but these were not sustained in conversational speech.

Videofiberoptic Laryngoscopy. There were no anatomical abnormalities noted although the ventricular folds seemed somewhat prominent anteriorly.

On exhalation during quiet respiration, intermittent, rapid spasmodic adductory movements were noted in the true vocal cords. Occasionally, the ventricular folds also moved to the midline anteriorly, although the speed of motion of these folds was not as rapid as that of the true folds. The ventricular fold motion again was evident on vowels particularly when they initiated the words. The displacement toward the midline was timed closely with the onset of the speech signal, and the folds were usually only momentarily maintained in the midline position. The ventricular fold movement was erratic in that it did not occur predictably on any phonetic task. The spasmodic movements of the true vocal cords during breathing and the ventricular fold movements during speech were not present in the videofiberoptic study of the normal larynx.

Use of a soft, breathy voice, a voice with an elevated vocal pitch level or a combination of both types of voices, always resulted in a lateralization of the position of the ventricular folds. This was true for simple phonatory utterances and during more extended utterances.

Case 2

A 55-year-old Caucasian female presented with a three-year history of hoarseness. The onset of hoarseness was surrounded by personal illness and emotional distress because of the death of a close friend of the patient. She noted that with time, talking became an effort and that she developed a dry feeling in her throat. She had been evaluated by three otolaryngologists, all of whom noted an anatomically normal-appearing larynx on indirect and direct laryngoscopy. Approximation at the midline of the ventricular folds was noted during one mirror examination of the larynx. The patient's voice gradually deteriorated to the point where there were never any instances of normal phonation.

Past medical history included irradiation for uterine carcinoma in 1949. In 1971 she saw a psychiatrist for chronic alcoholism. For a short time during her psychiatric care, she was treated with thioridazine, amitriptyline, and chlordiazepoxide. The patient claimed to be an epileptic, controlled with phenytoin and phenobarbital. She smoked 1.5 packs of cigarettes per day.

Physical Examination. The tense patient exhibited spontaneous grimacing of the face and pill-rolling of the left hand. The physical examination was otherwise normal.

Speech Evaluation. Extreme tension and strain were noted during phonation. The voice was characterized by hard glottal attacks, missed speech sounds, occasional mild grunts and voice stoppages. The patient was not always able to phonate immediately on command. There were also unexpected bursts of loudness and an excessively low vocal pitch which occasionally broke into a high-pitched, choked-sounding squeak. Aside comments and spontaneous laughter sometimes produced nearly normal phonation. Diadochokinesis was very poor. Neck muscle swelling and extreme engorgement of the veins in the neck were evident. Respiration for speech was tense and jerky. The patient denied having problems with mastication and deglutition. Only slight improvement in speech was noted with clinical stimulation.

Videofiberoptic Laryngoscopy. Marked supraglottic activity was noted in this patient. In addition to midline approximation of both the true and ventricular folds, marked constriction was noted in the oro- and hypopharynx. This latter feature, along with excessive secretions, restricted the number of observations that could be made in this patient. When the ventricular folds were displaced to the midline, the displacement occurred well before the onset of the speech signal and the folds remained in midline approximation until phonation eventually occurred. This appears to represent struggling behavior at the level of the larynx and probably accounts for the patient's inability to phonate immediately on command. Ventricular fold adduction of this severity was not seen in the study of the patient in Case 1. In all instances of phonation for the patient in Case 2, the true cords appeared to adduct and the adduction of the true cords always preceded that of the ventricular folds. A frontal and lateral contrast videofluoroscopic study was also performed on this patient corroborating the findings on the videofiberoptic laryngoscopy. In frontal projection, significantly increased ventricular fold activity was evident during breathing and phonation. A decrease in such activity was noted when the vocal pitch was raised or when the patient used a breathy mode of phonation. In lateral projection, marked constriction was seen in the oro- and hypopharynx and in the supraglottic area of the larynx. Soft, breathy phonation and elevation of the vocal pitch resulted in a widening of these areas of constriction.

DISCUSSION

Videolaryngoscopy demonstrates a number of advantages over indirect and direct laryngoscopy in visualization of the activity of the larynx: 1) the video feature of the system provides an enlarged image; 2) because the system utilizes flexible fiberoptics, it can be introduced transnasally so that minimal interference is imposed upon the motion of the structures of speech during extended utterances. Visualization during such utterances allows a more detailed observation of the functional dynamics of laryngeal structures. Thus, rather than observing the larynx during an isolated task such as "ah" or "ee," one is able to study the rapid temporal-spatial integration of activity of the larynx in the more natural situation of connected speech; 3) the patient can also be stimulated to produce a number of vocal maneuvers while the FFB is in place, making it possible to observe any improvements in laryngeal activity as a function of clinical stimulation.

Brewer and McCall[13] pointed out the advantages of viedofiberoptic laryngoscopy for voice therapy. Coupling the scope to a videotape system provided a permanent record of observations which could be reviewed repeatedly at a later date. It could also be played back immediately or simultaneously while recording so that the clinician or patient could observe events as they occurred. A biofeedback system could be facilitated with this approach which would allow the patient to monitor and attempt to adjust laryngeal activity during the performance of a variety of clinical speech tasks.

The disadvantages of the system are that it is expensive and requires the implementation of a more involved examination procedure. For some patients with spastic dysphonia, it is difficult to maintain the proper positioning of the distal end of the FFB during speech because of the marked tension along the vocal tract.

Activities of the larynx in the two cases presented consisted of spasmodic movements of the true vocal cord during exhalation (Case 2) and adduction of the ventricular folds during simple and extended utterances (Cases 1 and 2). The degree of medial compression of the true and ventricular folds at the midline could not be established using the techniques described herein. A very tight compression of the folds in adduction is certainly suggested by the momentary abrupt voice stoppages in Case 1 and the prolonged voice stoppages in Case 2. A tight compression would impose sufficiently strong resistance to the egressing airstream as to prevent vibration of the folds and thus, cessation of phonation. It might be speculated that in cases of dysphonia plicae ventricularis, adduction of the ventricular folds would also be seen with videofiberoptic laryngoscopy, but in contrast to spastic dysphonia, extremely tight medial compression probably does not occur. Characteristically, in dysphonia plicae ventricularis, uninterrupted phonation is more typical than either the prolonged or momentary vocal stoppages of spastic dysphonia.

It appears that both cases presented spastic dysphonia of the adductor type (Aronson classification). In neither of the two cases was a sudden abductory movement seen in the true vocal cords.

The results of this study corroborate several of the findings of McCall et al.[11] Using videofluoroscopy, these investigators noted tonic spasms of the larynx during quiet respiration, complete closure of the glottis and marked constriction of the ventricular folds and other structures of the supraglottic airway when voice stoppages occurred. In our study, videofiberoptic laryngoscopy revealed that adduction of the ventricular folds occurred in the anterior portion of these folds. It is to be noted that our fiberoptic observations focused upon laryngeal function. It is recognized that in some cases, according to the preliminary findings of McCall et al,[11] one may see unusual activity of the soft palate, tongue, and other structures along the vocal tract.

The therapeutic methods used by speech pathologists in the treatment of this disorder have developed empirically. The success of treatment has been based largely on an auditory assessment of the production of requested sounds and other maneuvers. Employing these time-honored methods, Fox[14] reported a case in which the vocal features of spastic dysphonia were successfully ameliorated by establishing a breathy voice quality. Cooper[3] asserted that establishing optimal vocal pitch level is vital in rehabilitating patients with spastic dysphonia. He advocates the elevation of vocal pitch for the majority of patients and utilization of such techniques as midsection breath support and minimization of vocal loudness. He reported that of 22 patients seen for voice therapy, 6 completed therapy. Of these six patients, one achieved excellent results, three achieved good results, and two achieved fair results.

Observations made in the present investigation of the laryngeal behavior in two cases of spastic dysphonia suggested that behavioral manipulation of the voice with spastic dysphonia can elicit improved vocal fold activity for phonation. Elimination of the hyperadduction of the true and false vocal folds was observed particularly when the patients minimized contact of the glottic margins of the vocal cords as in a breathy voice production, but also when vocal pitch was elevated. The behavioral approach to elimination of hyperadduction of the vocal folds for speech is a difficult process, however, and involves an extended period of therapy which may be only partially successful.

The amount of information available regarding laryngeal functioning in spastic dysphonia is meager. Further study of such function in spastic dysphonia with fiberoptic laryngoscopy would provide a better understanding of a disorder so frequently misdiagnosed as hysterical aphonia, dysphonia plicae ventricularis, or hyperfunctional dysphonia. Brodnitz[4] stressed the difficulties and pitfalls of establishing a diagnosis based upon overt visual symptomatology alone. These difficulties might be overcome, in part, by obtaining detailed visual information of laryngeal function. The techniques of fiberoptic laryngoscopy would then demonstrate the characteristic laryngeal behaviors associated with various voice disorders. In addition, pre- and post-treatment documentation of laryngeal activity in patients with spastic dysphonia would be obtained with fiberoptic laryngoscopy. This is particularly germane in view of the recent mode of therapy described by Dedo[15] where he has dramatically improved the voice in these patients by transecting the recurrent laryngeal nerve.

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SINUS HISTIOCYTOSIS WITH MASSIVE LYMPHADENOPATHY

REPORT OF ITS OCCURRENCE IN TWO SIBLINGS WITH RETROPHARYNGEAL INVOLVEMENT IN BOTH

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SUMMARY — Sinus histiocytosis with massive lymphadenopathy (SHML) was found in two siblings, both of whom had retropharyngeal involvement. In one of the children the retropharyngeal swelling appeared to produce obstructive symptoms, requiring excision of the involved lymph nodes. These cases appear to constitute not only the first proven familial occurrence of SHML but also the only reported instances of retropharyngeal involvement. SHML is an uncommon disease of unknown etiology that must be distinguished from other diseases associated with marked lymphadenopathy, particularly as its course is generally benign and not altered by any known form of medical treatment.

Sinus histiocytosis with massive lymphadenopathy (SHML) was first described in 1969 by Rosai and Dorfman[1] as a disease of unknown etiology occurring predominantly in the first decade of life and characterized by massive, nontender, cervical lymphadenopathy. Since then, a number of additional cases have been reported,[2-10] but the disease has received little or no attention in the otolaryngologic literature. Common clinical findings, in addition to the cervical lymphadenopathy, include enlargement of lymph nodes in other areas, particularly the mediastinum; fever; anemia; leukocytosis; elevated ESR; and, most characteristically, hypergammaglobulinemia. The microscopic findings in lymph nodes that define SHML as a pathologic entity consist of pericapsular fibrosis, dilatation of the sinuses, large numbers of plasma cells, marked proliferation of sinusoidal histiocytes containing clear cytoplasm, and the presence of lymphocytes and other hematopoietically-produced cells within the cytoplasm of these histiocytes. No form of treatment appears to alter the natural history of SHML, but eventual spontaneous regression has taken place in most reported cases, and many have resolved entirely.

The present report describes the occurrence of SHML, with prominent retropharyngeal involvement, in two siblings. These cases seem noteworthy in that neither proven familial occurrence of the disease nor involvement of retropharyngeal lymph nodes have been described previously.

CASE REPORTS

Case 1. L.H., a two-year-old Negro girl, was brought to the Children's Hospital medical clinic on February 24, 1971 because of swelling in the neck of six months' duration. Four months after onset she had received a three-week course of antibiotic treatment at another center, and this had been followed by excision-biopsy of a large, dumbbell-shaped mass from the left anterior cervical region. Otherwise, she had not seemed ill. Physical examination disclosed a 4.9 x 2.3 cm, nontender, firm, slightly movable mass just below the angle of the right jaw. No other abnormalities were noted; specifically, lymphadenopathy in other regions was not present. Pathologic diagnosis of the specimen removed earlier had not then been established; subsequently it was reported by the Armed Forces Institute of Pathology as "massive lymphoid hyperplasia consistent with a Rosai-Dorfman lesion (SHML)."

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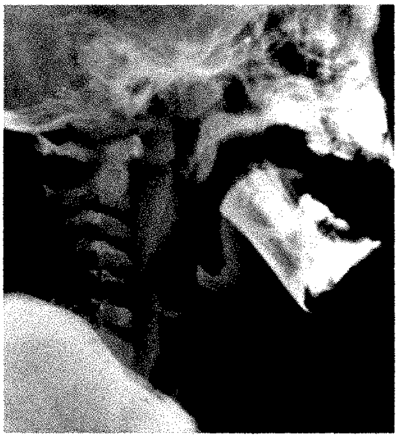

Fig. 1. (Case 1) Lateral roentgenogram of the neck revealing soft tissue density retropharyngeal mass.

A two-week regimen of oxacillin was prescribed, but one month later the mass had decreased in size only slightly if at all.

In November 1971, biopsy of the right cervical mass was carried out at another hospital; histopathologic examination confirmed the earlier diagnosis. Subsequently, massive lymphadenopathy in the left anterior cervical region recurred, and nasal breathing became noisy and apparently difficult. Tonsillectomy and adenoidectomy were performed at that hospital in August 1973; the histopathologic diagnosis was again reported as SHML.

Neither the upper respiratory obstruction nor the cervical lymphadenopathy improved, and coughing, gagging, vomiting, and weight loss developed. She returned to Children's Hospital for care, and an x-ray film of the neck in September 1973 showed a retropharyngeal mass (Fig. 1). Contrast studies showed anterior displacement of the hypopharynx and upper esophagus. Temporary worsening of symptoms was subsequently noted during episodes of upper respiratory infection. On March 28, 1974 she was admitted to the hospital. Laboratory studies disclosed the following values: Hb 12.0 gm%; hematocrit, 36%; WBC 7,100, with 68% neutrophils, 24% lymphocytes, 6% monocytes, and 1% eosinophils; total serum protein 10.2 gm%, of which albumin constituted 3.3 gm; α-1-globulin 0.4 gm (normal 0.2-0.3 gm), α-2-globulin 1.3 gm (normal 0.4-1.0 gm), β-globulin 1.5 gm (normal 0.5-1.0 gm), and γ-globulin 3.7 gm (normal 0.6-1.8 gm); serum IgG, 3,810 mg% (normal 942 ± 220); serum IgA, 384 mg% (normal 106 ± 47); and serum IgM, 436 mg% (normal 91 ± 39). Roentgenographic studies of the paranasal sinuses, chest, and upper gastrointestinal tract disclosed no abnormalities. An intradermal test for tuberculosis (intermediate strength PPD) was negative. On April 2, under general anesthesia, a left submaxillary lymph node was excised, and digital examination of the posterior pharyngeal wall confirmed the presence of a large retropharyngeal mass. Airway obstruction developed immediately postoperatively, and tracheostomy was performed the following day. On April 9 a retropharyngeal mass measuring 5 cm in diameter was excised; histologic examination of the specimen demonstrated findings typical of SHML (Fig. 2). On April 16 the tracheostomy tube was removed without recurrence of respiratory difficulty, and on April 18, 1974 she was discharged from the hospital.

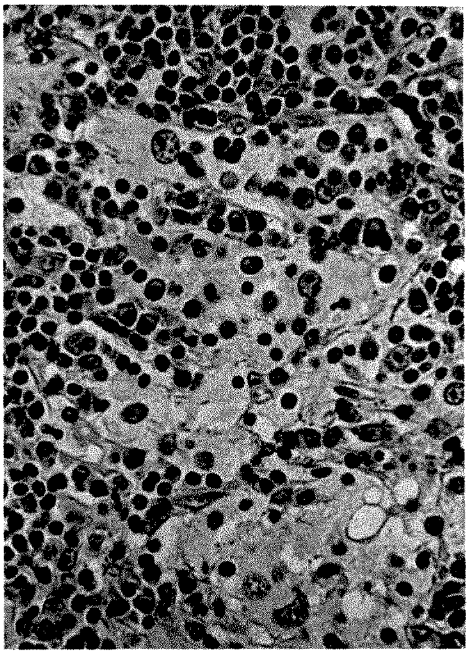

Fig. 2. (Case 1) Numerous mature lymphocytes and plasma cells are present in the intersinusoidal stroma and sinusoids (H & E, X 240).

She was not seen again until January 20, 1976, when she was brought to the emergency room because of having vomited during the preceding day. She did not seem appreciably ill, and examination disclosed no evidence of cervical lymphadenopathy, retropharyngeal swelling, respiratory obstruction, or enlargement of the liver or spleen. She was not examined subsequently, but at current writing is reported by her mother to be well.

Case 2. G.H., a three-year-old Negro boy, was brought to the Children's Hospital emergency room on August 26, 1975 because of swelling in the neck said to have been present intermittently for two years, especially in association with upper respiratory infections. He had often received antibiotic treatment which seemed each time to induce temporary improvement. Otherwise he had been in good health. Tuberculin tine tests administered on two occasions were said to have been negative.

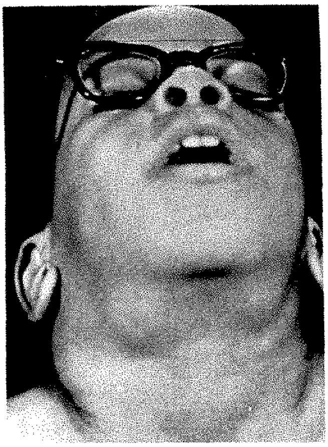

Fig. 3. (Case 2) Three-year-old boy with massive cervical lymphadenopathy.

Physical examination disclosed numerous rubbery lymph nodes, ranging in diameter from 2 to 5 cm, in the anterior and posterior cervical regions bilaterally. The submandibular and postauricular nodes were the most prominent. There was no enlargement of other lymph nodes or of the liver or spleen. The WBC was 6,600 with 68% neutrophils, 20% lymphocytes, 11% monocytes, and 1% eosinophils. A tuberculin tine test was administered and was later reported as having been negative. A ten-day course of treatment with erythromycin was prescribed.

He did not return for follow-up, but was seen six weeks later in the emergency room because of an acute asthmatic episode. Cervical lymphadenopathy was again noted, and expiratory wheezes were heard throughout the chest. A heterophil antibody titer was not elevated. Epinephrine was administered subcutaneously and the wheezing promptly improved. A ten-day course of penicillin and Marax® was prescribed, and he was referred for further study to the T & A Clinic,[11] where he was first seen on December 30. Examination there revealed no change in the previously noted cervical lymphadenopathy (Fig. 3). No difficulty in nasal breathing was apparent, and the tonsils were small. There were no other abnormal findings. Successive two-week courses of penicillin and erythromycin were administered during a period when various studies were being obtained. Noteworthy among the results of these were the following: WBC 6,900, with 63% neutrophils, 4% bands, 13% lymphocytes, 9% monocytes, and 11% eosinophils; serum IgG, 2,100 mg% (normal 872 ± 145); serum IgA, 153 mg% (normal 123 ± 60); and serum IgM, 173 mg% (normal 64 ± 20). An x-ray film of the neck showed a soft tissue density retropharyngeal mass (Fig. 4). Films of the skull and long bones were negative.

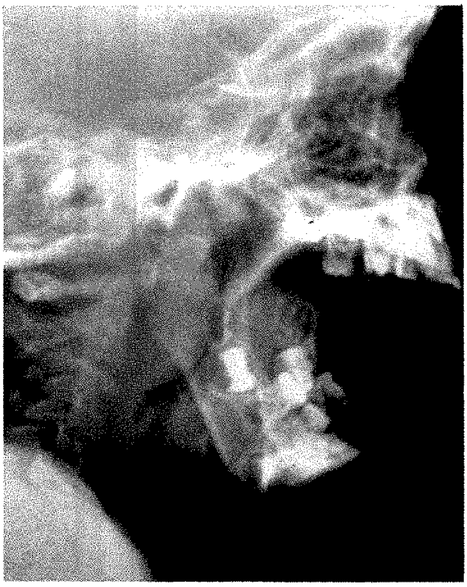

Fig. 4. (Case 2) Lateral roentgenogram of the neck revealing soft tissue density retropharyngeal mass.

The lymphadenopathy failed to subside and a bulge was noted in the right side of the posterior wall of the pharynx. The patient's mother was advised that cervical lymph node biopsy would be necessary. She responded with agitation, "You're not trying to tell me that he has Rosai-Dorfman disease just like my daughter!" — and then provided a detailed account of L.H.'s illness, indicating that she had until now deliberately withheld this information out of fear that disclosing it might have precipitated an operative procedure on G.H. She stated a belief that L.H.'s episode of respiratory obstruction and subsequent tracheostomy might have been avoided if her retropharyngeal tumor had been excised earlier, and stated further that she would consent to a surgical procedure on G.H. only if it were to include removal of his retropharyngeal tumor.

Studies carried out preliminary to operation gave the following values and results: Hb 10.7 gm%; WBC 7,800, with 62% neutrophils, 27% lymphocytes, 6% monocytes, 4% eosinophils, and 1% bands; ESR 41 mm per hour; serum IgG, 1500 mg%; serum IgA, 145 mg%; serum IgM, 115 mg%; the phytohemagglutinin stimulatory index[12] was 26 (normal ≥ 40) in heterologous (Type AB) plasma, and 94 in autologous (Type 0) plasma; the nitroblue tetrazolium (NBT) test score was elevated, with 5102 NBT-positive neutrophils per ml, and the percentage of such cells 61: a latex fixation test for *Histoplasma* was negative; the third and fourth serum complement components were normal, with C_3 145 mg% and C_4 35 mg%; the T-cell count as determined by sheep erythrocyte rosette formation was 589 (normal 1160 ± 389) per ml. Repeated cultures of the nose and throat were negative for viruses and for bacterial pathogens. Delayed hypersensitivity skin tests in concentrations of 1:1,000 were positive at 48 hours for mumps, but negative for *Candida*, streptokinase-streptodornase, and tetanus.

On February 5, 1976, a mass in the neck, thought to be anterior cervical lymph nodes, was excised, and the retropharyngeal mass was resected. The histopathologic findings in both specimens were indicative of SHML, but the tissue removed from the neck proved to have been extensively involved salivary gland, rather than lymph nodes. Cultures of the specimens for bacteria, including mycobacteria, were negative except for an occasional colony of coagulase-positive staphylococcus; and cultures for fungi and viruses were also negative.

During a nine-month period following operation the patient remained asymptomatic, but continued to have extensive cervical lymphadenopathy and slight prominence of the right posterior pharyngeal wall. On April 12, 1976 he was vaccinated against rubella, and five months later the rubella antibody titer was 1:160, which is an expected level for an immunized child. His mother has been unwilling to permit additional immunologic studies.

DISCUSSION

The two cases reported here call attention to SHML as an apparently uncommon, pseudolymphomatous disease that must be distinguished from other conditions found mainly in children and associated with marked enlargement of cervical lymph nodes.[13] Previously reported reviews[1,2] have detailed the known clinical and epidemiologic features of the disease; to these must now be added 1) involvement of retropharyngeal lymph nodes and 2) occurrence in siblings.

Although the etiology of SHML is unknown, certain evidence suggests that an abnormal immune response to an infectious agent or agents may be involved in its pathogenesis. Specifically, transient immunologic defects were described in one infant with the disease,[5] while in other patients markedly elevated hemagglutination inhibitation titers following the administration of rubella vaccine,[4,9] and elevated titers against various Epstein-Barr virus antigens,[2,4] have been reported. The patient in Case 2 had a normal antibody response five months following rubella immunization, and no definite immunologic abnormalities were disclosed by the various studies he received. The high concentrations of serum immunoglobulins found in patients in both Cases 1 and 2, and in many other patients with SHML, are compatible with the presence of an underlying immunological abnormality, but on the other hand, merely may be by-products of the disease itself or secondary to chronic infection. If an immunologic abnormality is involved in the pathogenesis of SHML, the occurrence of the disease in siblings —with similar ages of onset and strikingly similar sites of involvement—suggests that it may be genetically transmitted.

It would appear that treatment for SHML should be limited to measures directed at relieving obstruction when it occurs, as in Case 1. No known form of medical treatment appears to alter the natural history of the disease, and its course has generally been benign, characterized by spontaneous regression, and in many instances, complete resolution. It seems important to note, however, that three patients with SHML are known to have died—one of renal amyloidosis; one with bilateral necrotizing *Pseudomonas aeruginosa* bronchopneumonia following treatment with radiation, steroids and chemotherapeutic agents; and one of undetermined cause.[2]

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The Association of Otolaryngologists of India will be holding its 31st Annual Conference at Nagpur January 11-14, 1979. For further information please contact: Dr. P. P. Karnik, Hon. Secretary, K.E.M. Hospital & G.S. Medical College, Bombay, India 400012.

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HEAD AND NECK MANIFESTATIONS OF SCLERODERMA

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SUMMARY — Scleroderma has rarely been discussed in the otolaryngologic literature. A review of the records of 71 scleroderma patients admitted to UCLA Hospital during the past five years indicates that head and neck manifestations are common, occurring in 80% of these patients. The initial symptoms in 30% among them were related to the head and neck. It is the purpose of this paper to familiarize otolaryngologists with scleroderma. Although it has not been emphasized in the past, this is a disease whose early symptoms and findings may require otolaryngologic consultation and whose later course is characterized by head and neck symptoms and findings in the overwhelming majority of patients.

Scleroderma is a relatively uncommon and incompletely understood disease. Because it shares features with systemic lupus, dermatomyositis, polymyositis, rheumatoid arthritis, and polyarteritis nodosa, it has been placed in the category of connective tissue disorders. The diagnosis of scleroderma is based on specific clinical criteria, but it may take several years for the symptoms of the disease to evolve sufficiently to differentiate it from other disorders.

GENERAL ASPECTS

The name scleroderma (literally, hard skin) derives from the sometimes striking cutaneous manifestations. Areas of the face, neck, trunk, and extremities are commonly affected in varying distributions of skin. Changes proceed from initial edema to thickening and smoothness, and finally to fixation and firmness as the skin becomes bound to underlying fibrotic subcutaneous tissues.[1] Calcinosis of soft tissues is not uncommon. In addition to generalized scleroderma, several terms have been used to describe patterns of cutaneous involvement: CRST syndrome (calcinosis, Raynaud's phenomenon, sclerodactyly, and telangiectasis), acrosclerosis (marked involvement of distal extremities), and Thibierge-Weissenbach syndrome (extensive subcutaneous calcinosis). These patterns might be considered variants of scleroderma, inasmuch as all can be associated with the systemic manifestations of the disease. On the other hand, lesions of morphea and linear scleroderma are purely cutaneous, lack visceral involvement, and should be considered different from scleroderma.

Although cutaneous involvement may be striking, it is not necessarily an initial feature of the disease.[2] Goetz was the first to recognize the systemic nature and visceral involvement in scleroderma, and used the words "progressive systemic sclerosis" to describe the disorder more accurately.[3] This term has gained popularity today, although some authors prefer "systemic sclerosis," noting a lack of progression in some cases. Noncutaneous involvement may be either minimal or extensive, and can precede skin changes by years. Raynaud's phenomenon is often present many years before other changes are noted. Gastrointestinal, cardiovascular, pulmonary, and renal involvement account for the most serious manifestations of the disease. Severe disability and even death can result from cardiac failure, arrhythmias, pericarditis, pulmonary failure, anemia, malabsorption with cachexia, gangrene of digits, and hypertension.

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TABLE 1. AGE, SEX, AND DURATION OF SYMPTOMS

	Male	*Female*
Number of patients	14	57
Mean duration of symptoms in years	8.4	8.8
Mean age	45.4	47.4
Age range	22-61	21-79

Despite such protean manifestations, the etiology of scleroderma remains obscure. Infectious, genetic, toxic, immunologic, vascular, and even psychologic factors have been invoked, but none appear adequate to explain the pathogenesis.[4] Histopathologically, small arteries, arterioles, and capillaries of affected organs show intimal thickening, sometimes with medial sclerosis and fibrinoid change. Although it should be noted that such histologic changes are not specific for scleroderma, these pathologic findings and certain clinical features appear to relate scleroderma to other forms of vasculitis and connective tissue disease. Indeed, positive antinuclear antibodies and rheumatoid factors are not uncommon in scleroderma. Thus, despite the unknown etiology of scleroderma, it is probably similar to that of other collagen vascular diseases.

METHODS AND MATERIALS

In order to determine frequency and type of otolaryngologic manifestations of scleroderma, the inpatient records concerning 71 scleroderma patients hospitalized at UCLA Hospital during the period from January 1, 1970 to December 31, 1975 were reviewed. Only those patients admitted for treatment or evaluation were included; patients whose diagnosis of scleroderma was considered but uncertain, or who manifested a "crossover syndrome" or "mixed collagen disease" were excluded from the study. Criteria for inclusion in the series required that the patients be assigned a positive diagnosis of scleroderma according to guidelines set forth by Medsger and Masi.[5] All records were reviewed by the authors, with particular attention to initial symptoms referable to the head and neck, in addition to similar symptoms occurring throughout the course of the disease.

RESULTS

The distribution of our patients with respect to age, sex, and duration of symptoms is presented in Table 1. As in most other reported series, middle-aged females predominated. Of the 71 patients studied, 57 (80%) had symptoms or findings referable to the head and neck at some time during their disease (Table 2). Thirty-two patients (31%) had *presenting* symptoms in the head and neck region (Table 3).

TABLE 2. TOTAL HEAD AND NECK SYMPTOMS AND FINDINGS

Symptom Category	*%*	*No.*
Cutaneous		
Tight facial skin	35	25
Telangiectasias (9 cutaneous, 4 mucous membrane)	18	13
Facial hyperpigmentation	7	5
Calcinosis	3	2
Total		45
Upper gastrointestinal		
Dysphagia (14 with abnormal esophagram)	39	28
Esophageal stricture	8	6
Abnormal esophagram with no symptoms	30	21
Total		55
Oral		
Decreased mouth opening	28	20
Scleroderma plaques of tongue	1	1
Decreased sense of taste	1	1
Total		22
Sicca syndrome		
Xerostomia	8	6
Keratoconjunctivitis sicca	3	2
Parotitis	1	1
Total		9
Miscellaneous		
Neck stiffness, fullness or pain	14	10
Voice changes	6	4
Total		14

Initial Symptoms. The most common otolaryngologic presenting symptom was dysphagia, observed in 16 patients (52%); the second was decreased mouth opening, which appeared in 6 patients (19%). A variety of other head and neck presenting complaints were recorded,

TABLE 3. PRESENTING SYMPTOMS AND FINDINGS

Symptom	*No.*	%
Dysphagia	16	52
Decreased mouth opening	6	19
Neck stiffness, fullness or pain	4	13
Hyperpigmented face	2	6.5
Voice changes	2	6.5
Decreased taste	1	3
	31	100

most notably in four patients suffering with a painful and stiff neck, and two who experienced voice changes.

Total Incidence of Head and Neck Symptoms and Findings. Among patients who developed head and neck manifestations, multiple symptoms and findings were the rule. The major single symptom was dysphagia, found in 27 patients (39%). Thirty-five (49%) of the patients had an abnormal esophagram; of these, only 14 had dysphagia. Thus, 40% of patients with an abnormal esophagram were symptomatic. On the other hand, of the 27 patients with dysphagia, 13 (or roughly half) exhibited normal esophagrams. In this connection, it should be noted that virtually every patient in our series had an esophagram. Cutaneous findings were likewise common, with tight facial skin apparent in 25 (35%), and head and neck telangiectasias present in 13 (18%). Decreased mouth opening occurred in 20 (28%) of the patients.

Less frequent findings were manifestations of a sicca syndrome in 12%, esophageal stricture in 8% and voice changes in 6% of the patients. Various other head and neck symptoms and findings that were occasionally encountered are listed in Table 2. At least seven of the patients in this series are known to have died during the period reviewed; however, this should not be taken as an indication of the mortality rate in scleroderma, since complete follow-up data were unavailable for every patient, and not all deaths were necessarily a direct result of scleroderma. Indeed, in only one instance was the cause of death possibly related to an otolaryngologic problem, and that patient died of aspiration pneumonia as a complication of esophageal dysfunction. Although it may be an incidental finding, it is worth mentioning that another patient died of carcinoma of the esophagus.

DISCUSSION

An analysis of the data derived even from a retrospective study indicates that patients with scleroderma often manifest symptoms or findings referable to the head and neck region. It is also evident that a significant percentage suffer presenting symptoms that may cause them to seek the attention of an otolaryngologist. Despite these facts, scant attention has been paid to scleroderma in the literature of our specialty.[6]

Dysphagia. Dysphagia, the most frequent otolaryngologic complaint in our series, has long been recognized as a prominent feature of scleroderma. Although esophageal abnormalities are often striking radiographically, they do not correlate well with dysphagia in scleroderma. In our series, 21 of 35 patients (60%) with abnormal esophagrams did not experience dysphagia. Of 27 patients with dysphagia, only 14 (53%) had an abnormal esophagram. These statistics compare favorably with the experiences reported by other authors.[7,8]

The classic roentgenologic finding in scleroderma is the inability of the esophagus to empty without the aid of gravity (Fig. 1). According to Lorber's study, peristaltic waves were weak or absent in 81%, dilatation at various levels occurred in 51%, and lower esophageal strictures were present in 6% of scleroderma patients.[9] Manometric studies have shown that there is generalized loss of contractile power except at the cricopharyngeal region.[4] The esophagogastric sphincter is usually incompetent, and it has been postulated that the lower esophageal strictures in scleroderma often stem from chronic reflux peptic esophagitis. In our series, 6 of the 71 patients had lower esophageal strictures, 4 of which required dilation.

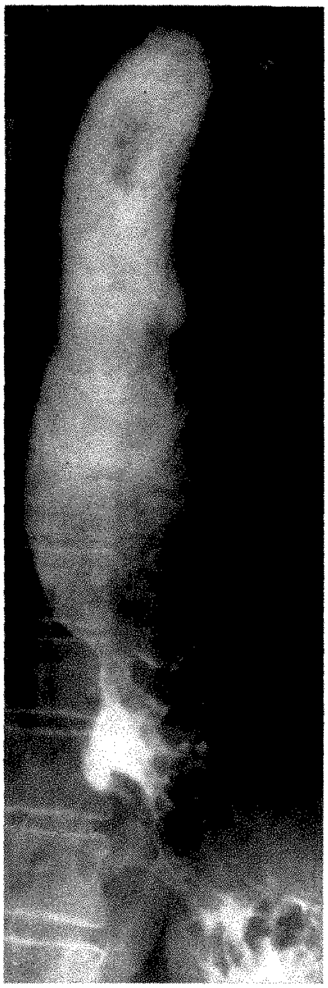

Fig. 1. Esophagram of patient with scleroderma demonstrating lack of emptying, absence of peristaltic waves, and dilatation of distal esophagus proximal to a lower esophageal stricture.

Lindsay has reported esophagoscopic findings in scleroderma.[10] The mucosa may be pale, stiff, and thrown into coarse folds. Exudation and ulceration of the distal esophagus are common, and stricture may also be encountered. The distal esophagus may be shortened from scarring, and the stomach may be pulled through the diaphragmatic hiatus. Although perforation of the esophagus during esophagoscopy has been reported, there is no evidence of an increased risk of perforation in these patients, nor is there reason to believe that they have an increased probability of developing carcinoma of the esophagus[4] (even though one of our patients died of this condition).

Another factor that may contribute to dysphagia is the appearance of abnormalities in the tongue and pharynx. It has been reported that the tongue is often affected in scleroderma, principally by formation of mucosal plaques and by muscular atrophy.[11] One patient in our study displayed this finding and had dysphagia. Cineroentgenographic techniques have been used to show that the difficulty in swallowing experienced by many patients may stem from incoordination and abnormal movements of the tongue. Failure of palatoglossal closure has been demonstrated in this way. A large residual bolus of barium is often seen in the hypopharynx, and multiple swallowing movements are required to pass it into the esophagus. Despite these observations, aspiration of barium is rarely seen.[12]

It would thus appear that the dysphagia characteristic of scleroderma is probably based on motility disturbances of the tongue, pharynx, and esophagus, rather than on specific structural abnormalities. Cineroentgenographic procedures probably demonstrate this type of problem better than routine contrast studies. Nevertheless, in spite of radiographic, manometric and histopathologic studies, the etiology of upper gastrointestinal dysfunction remains unclear.

Cutaneous Manifestations. Cutaneous manifestations in our series consisted of tight facial skin and telangiectasias of the face and mucous membranes. While these were among the commonest findings, they were never encountered as presenting symptoms. In the past, facial and mucous membrane telangiectasias have received attention because of the similarity to those seen in Osler-Weber-Rendu disease (Fig. 2). Macroscopically, the lesions are identical, and in Winterbauer's original description of seven patients who had scleroderma with telangiectasia, three also had epistaxis.[13] According to Barnett, although telangi-

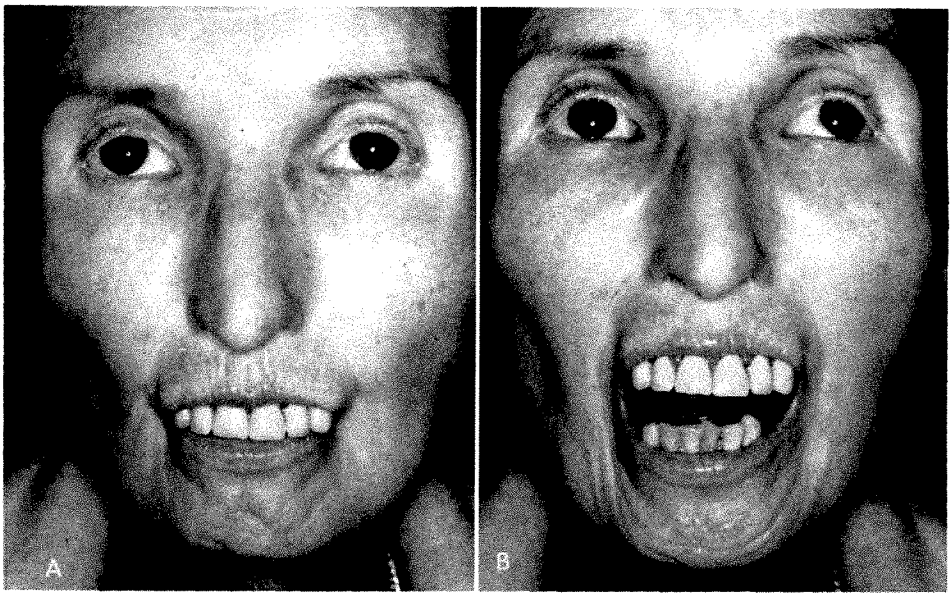

Fig. 2. A) Typical facies of scleroderma with numerous facial telangiectasias; smoothness and loss of lines of facial expression are apparent. The oral aperture is decreased in size, causing the anterior teeth to protrude. B) Demonstration of decreased mouth opening.

ectasias are common, bleeding is usually not a problem.[14] We found this to be the case in our series, in which only one of 13 patients with telangiectasia had epistaxis. Marked female predominance, absence of severe bleeding, and lack of familial occurrence serve to distinguish scleroderma from Osler-Weber-Rendu disease.

Oral Manifestations. Inability to open the mouth is a common and distressing problem in scleroderma. It may result from temporomandibular joint dysfunction, but probably is secondary to changes in the perioral soft tissues. A characteristic "fish-mouth" appearance is caused by contraction of the oral aperture (Fig. 2). Decreased mouth opening of varying degrees was present in 20 patients (28%) in our series. One patient of particular interest required a commissurotomy to create an adequate mouth opening. Results of preliminary EMG studies indicate that in some patients, true trismus with temporalis or masseter spasm takes place. However, this does not appear to be the etiology of diminished mouth opening in most cases.*

With regard to the temporomandibular joint, it should be noted that arthralgias and joint stiffness giving a picture of nonmigratory polyarthritis occur often in scleroderma. Radiographic and histologic changes in all affected joints (including the temporomandibular) are minimal, usually consisting of mild synovitis without proliferation or pannus formation. On the other hand, inflammatory reaction and synovial fibrosis are common. Sackner commented that true temporomandibular joint arthritis is very rare in scleroderma and that decreased mouth opening is usually caused by soft tissue changes.[4] A significant number of patients in our series appeared to have temporomandibular joint dysfunction, manifested by ear pain, popping, and actual temporomandibular joint stiffness. The majority exhibited decreased mouth opening secondary to soft tissue changes, however. Radiographic studies of the temporomandibular joint were not performed in most of the patients, so that an objec-

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*Ross M: Personal communication.

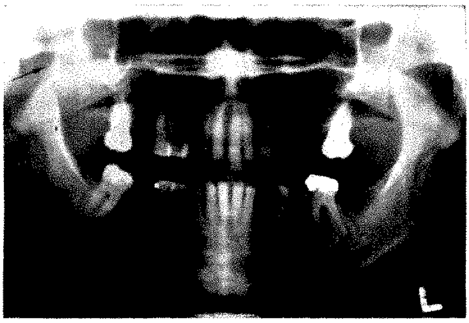

Fig. 3. Panoramic radiograph of the mandible in a patient with scleroderma, demonstrating osseous resorption of both mandibular angles and ascending rami (lower arrows). The right coronoid process apparently has been amputated and partially destroyed by the same osseous resorptive process (upper arrow). The impacted right mandibular canine tooth was an incidental finding. (Radiograph courtesy of S. C. White, DDS, UCLA School of Dentistry.)

tive assessment of joint involvement is unavailable.

Certain oral radiographic changes in scleroderma have been well described. Thickening of the periodontal membrane, demonstrable in more than a third of these patients, is a potentially reversible lesion, not associated with loosening of the teeth, and usually affects the posterior teeth.[15]

Resorption of the mandibular angles and destruction of the coronoid process, first noted by Taveras[16] and later reported by Seiffert et al,[17] is a rarer phenomenon. Weber et al[18] described a patient with this finding who suffered bilateral angle fractures after minimal trauma. A recently concluded prospective study from our institution concerned resorption of mandibular angles in 6 of 36 cases of scleroderma,* two of which showed progressive resorption, one to a marked degree (Fig. 3). These patients should probably be considered at risk for pathologic fractures.

The mechanism of this bone resorption is unknown. Resorption of distal phalanges, clavicles and ribs also occurs in scleroderma, and these phenomena may have a similar mechanism. Hypothetical explanations have included vascular insufficiency, alterations within the bones and changes secondary to overlying tight skin. It has been demonstrated, however, that this bone resorptive process in scleroderma is not necessarily associated with overlying tight skin nor with vascular insufficiency.

Sicca Syndrome. Features of a sicca syndrome were present in 12% of the patients in our series (Table 2), but in no case were these presenting symptoms. In the past, Sjogren's syndrome, a disorder characterized by sicca symptoms, has been known to have an occasional association with scleroderma.[14] One large representative series reported scleroderma in 5% of Sjogren's patients.[19] Another prospective study evaluated 25 consecutive patients with scleroderma for evidence of Sjogren's syndrome.[20] Clinical examination, Schirmer's test, rose bengal staining, parotid sialography, ^{99}M Tc pertechnetate scanning, radionuclide salivary excretion tests, and lip biopsies to study minor salivary glands were performed. Using this extensive battery, all 25 patients had at least one abnormal test result, and all but three had two or more abnormal results. Of these tests, clinical evaluation, parotid sialography, and lower lip biopsies for minor salivary gland histology were the most helpful. Thus it would appear that a higher than previously appreciated percentage of patients with scleroderma reveal features of Sjogren's syndrome, although in many it may be subclinical and demonstrable only via special diagnostic tests.

Other Findings. While it is noteworthy that four patients in our series presented with neck pain, stiffness or fullness, not enough information is available to relate this more than coincidentally to the course of the disease. The same is true of the patient who presented with a decreased sense of taste (Table 2). Two patients presented with voice changes, and two others noted such changes during the course of the disease. In only one case was the etiology of voice change determined by laryngoscopy, a patient who had edema of the arytenoids and pyriform sinus, although biopsy showed only edema. It could be speculated that the larynx might be a target organ in scleroderma either through soft tissue or neuromuscular involvement. In a review of 24 patients with laryngeal edema of obscure origin, Calcaterra[21] reported two with systemic lupus, one with polyarteritis, and one with severe rheumatoid arthritis, all conditions closely related to scleroderma.

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*White SC: Personal communication.

An abnormal vocalization called the "scleroderma bark" has been described in the past.[22] Patients with this symptom produce an involuntary vocalization approximately every two hours during the day. It has been postulated on the basis of x-rays that aerophagia in the presence of an incompetent esophagogastric junction causes air to be expelled suddenly, rushing past the cricopharyngeal sphincter and thereby producing this involuntary sound.

CONCLUSIONS

Scleroderma is an unusual disease with protean manifestations, many of which are related to the head and neck. Surprisingly, it has received almost no attention in the otolaryngologic literature. A retrospective study was made of the records of 71 patients with scleroderma who were hospitalized over a five-year period, and it revealed that 80% had symptoms referable to the head and neck. In 31% of the patients these were among the presenting symptoms. Dysphagia proved to be the chief symptom, both initially and throughout the course of the disease. Cutaneous changes such as tight facial skin and telangiectasia also occurred frequently but were never presenting symptoms, nor were telangiectasias generally associated with epistaxis. Decreased mouth opening, usually secondary to perioral soft tissue changes, was found often and was a presenting complaint in 19%. Findings of a sicca syndrome were evident in 12% of our patients but were not presenting symptoms. Various other symptoms and findings of indeterminate significance were also noted.

It would appear on the basis of our study of this group that scleroderma is a disease with numerous major otolaryngologic manifestations. Not only is it likely that some undiagnosed patients suffering from scleroderma will seek consultation with an otolaryngologist, but most will develop symptoms during the course of their disease that should attract his attention, and about which he should be informed.

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NATIONAL HEARING ASSOCIATION

The National Hearing Association, a newly formed, not-for-profit foundation dedicated to the cause of cure and prevention of deafness, opened its national headquarters offices at 1010 Jorie Boulevard (Suite 308), Oak Brook, IL 60521 on February 3, 1978. Some of the country's leading otologists and interested business and community leaders are emphasizing the fact that funds available to support research for the cure and prevention of deafness are far less than funds devoted to other handicaps that affect a much smaller percentage of the population. The National Hearing Association is dedicated to correcting this deficency in research funding.

Mr. M. A. Self is Chairman, George E. Shambaugh, Jr., MD is President and J. William Wright, Jr., MD is 1st Vice-President of the Association.

Those interested in helping the National Hearing Association by becoming active members and/or assisting in chapter development, fund raising, and other activities are urged to write: National Hearing Association, 1010 Jorie Boulevard (Suite 308), Oak Brook, IL 60521.

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COMBINED FLAP-WIRE RECONSTRUCTION OF THE ORAL CAVITY

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SUMMARY — The concept of immediate reconstruction for head and neck defects following tumor resection provides the impetus for the development of new reconstructive techniques. In this article, the authors describe the evolution of local and regional flaps and the more recent use of composite tissues. The application of a combined forehead-deltopectoral flap and Kirschner wire for the reconstruction of a large defect involving the oral cavity, mandible and facial-cervical skin is presented in a case report and evaluated as to its efficacy in the treatment of head and neck cancer.

During the last century advances in surgical techniques, nutritional support, blood transfusions, and antibiotics have allowed the resection of sizable tumors of the oral cavity and subsequent reconstruction of the surgical defects.[1-3] The long-held philosophy of "wait and see," where repair is delayed until there is no evidence of recurrent cancer has given way to one of immediate reconstruction. The "oral cripple"[4] is to be avoided, and the surgeon strives for early speech, deglutition and acceptable appearance. Common goals are to restore facial contour and to provide support and mobility to the lips, tongue, and larynx.

The purposes of this paper are to review the various techniques utilized for reconstruction of the oral cavity, and to present a combined flap-wire approach for immediate restoration of defects of the floor of the mouth, mandible, tongue, and cheek. Various reconstructive techniques are discussed from the standpoint of available tissues, flap viability and the support provided for adjoining structures.

LITERATURE REVIEW

Small defects of the oral cavity can be treated with skin grafts, local flaps or direct approximation of residual tissues. Popular flaps have been derived from the tissues of the tongue and nasolabial folds. The central portion of the tongue[5] may be advanced, or the filleted lateral or anterior margins may be transposed into the defect.[6] Nasolabial flaps, based on the angular branch of the facial artery, can be rotated to repair small areas of tissue loss.[7]

For the larger defects, seen after resection of extensive tumors, regional or distant flaps have been used for repair. The amount of tissue necessary for reconstruction can occasionally be minimized by combining resection of the mandible with excision of the cancer, but still a sizable defect may remain. In these cases the forehead, deltopectoral, and anterior, lateral, and nape of neck flaps, all of which obtain their arterial blood supply from major vessels, can be used for restoration of the surgical defect.

McGregor's forehead flap, based on the frontal branch of the superficial temporal artery, has been one of the more popular techniques.[8] By including the posterior auricular vessels in the pedicle, the flap can be elevated from the entire forehead and transferred without a prior delay.[2] The flap may be rotated into the mouth via a tunnel

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created either lateral or medial to the zygoma.[8,9] The subzygomatic transfer spares needless trauma to the facial nerve branches, but this route may be plagued by constriction of the flap pedicle.[10,11] The flaps are particularly useful for transposition and repair of full thickness cheek defects when underlined by a split-thickness graft.

Cervical flaps have also been frequently used in the repair of the oral cavity. A laterally based, skin-lined cervical flap, described by Blair,[12] may be applied to close large defects of the cheek. Littlewood[13] has reported a cervical flap for postmaxillectomy reconstruction which is based on the occipital and posterior auricular vessels to include full-thickness cervical skin, platysma and sternocleidomastoid muscle. Another superiorly and laterally based flap for oral reconstruction has been described by Bakamjian and Littlewood[14] with the option of transferring a chest flap into the cervical defect. Poisson and Franchebois[15] have recently designed a triangular cervical flap, based superiorly on the external jugular vein, but this flap is only recommended for small intraoral mucosal repairs. Zovickian[16] has popularized a staged anterior cervical flap of the apron-type based on branches of the facial artery. Others have recommended the posterior cervical flap or "nape of the neck" flap, of which the vascular supply is the occipital and posterior auricular arteries, but transfer requires at least one delay to enhance viability in a previously operated or irradiated field.[17]

The deltopectoral flap of Bakamjian and Marshall[18] has also proved useful in reconstruction of the oral cavity, lower face and neck areas. It is usually based on the perforating branches of the internal mammary artery, but can be based laterally on the acromioclavicular artery. In this latter design, a delay is strongly recommended to improve survival.

For reconstruction of the mandible, various methods have been described utilizing wires, plates, pins and grafts. Millard[2] has suggested a technique of cortical hip or rib autograft stabilized by interosseous wiring and Kirschner wires. Others have advocated autogenous iliac crest bone chips and a vitallium or stainless steel mesh.[19-22] Alvarado and associates[23] have reported replacement of the jaw with autoclaved autogenous mandible removed from the patient after resection of the specimen. Kirschner wires supporting a silastic block have been used by McQuarrie[24] and Yonemoto[25] in nonirradiated patients; while others[26] have used Kirschner wires alone for retaining mandibular contour and function. Mesh trays made of a variety of materials, stainless steel, titanium, silastic and dacron, have been successful when used singly or with cancellous bone. Choice of methods has been dependent primarily upon the degree of irradiation, the amount of bone and site of bone to be replaced, availability of soft tissues and the needs of the patient.

In patients where reconstruction of multiple structures is necessary, combinations of techniques have also been employed. Full-thickness defects of the cheek have been corrected by a combination of tissues where one flap forms an internal surface and the other, an external surface.[3,12,13] Conley[27] has presented a case in which the forehead flap was used for an internal buccal graft and a chest-rib flap for skin and mandibular reconstruction. Complications apparently did not occur if the transfer was limited to 15-20 cm of clavicle or rib. The method of combining cervical flaps and the experience with implants has provided an opportunity to extend these techniques to the rehabilitation of patients requiring repair of extensive defects involving the oral cavity, mandible, and facial skin.

CASE REPORT

In July 1975, an 82-year-old blacksmith complaining of pain and choking when swallowing was found to have squamous-cell carcinoma of the right tongue and floor of the mouth. The patient was treated with 4000 rads of Cobalt^{60} with resolution of symptoms. Six months later, a right superior cervical node was noted and an additional 2000 rads of Cobalt^{60} was administered to the neck area. An orocutaneous fistula developed and x-ray evaluation showed marked mandibular destruction.

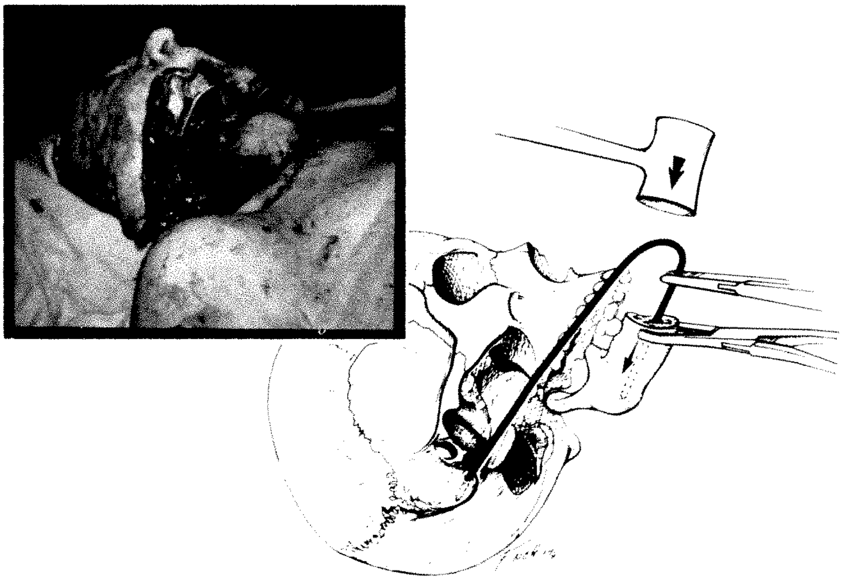

Fig. 1. Insertion of Kirschner wire in jaw fragments and mastoid tip.

On evaluation at the Hennepin County Medical Center the fistula was approximately 2 cm in diameter with the tumor extending intraorally from the right canine tooth to the retromolar trigone. The lesion included the buccal mucosa and the lateral third of the tongue. The right superior cervical area contained a 3 cm group of matted lymph nodes. Further evaluation showed a small pulmonary nodule consistent with metastatic disease in the right midlung field.

After deliberation and discussion of the various methods of treatment, it was decided to palliate the patient with resection of the cancer and immediate reconstruction. The rationale for this approach was that the lung lesion would not be incapacitating for at least six months to a year, but that the patient would be severely disabled by a painful, enlarging fistula.

On June 15, 1976 forehead and deltopectoral flaps were delayed in preparation for excision of the carcinoma and reconstruction of the oral cavity.

The deltopectoral flap was developed with the arm and shoulder in a neutral position from parallel chest incisions which encompassed four perforating branches of the internal mammary artery. The upper incision followed the clavicle across the acromion to the lateral deltoid area, while the lower incision passed above the anterior axillary fold to join the lateral extent of the upper incision. Elevation was carried out deep to the fascial plane over the pectoralis major muscle, releasing the entire flap. A light pressure dressing and drains were applied to prevent hematoma formation.

The forehead flap was elevated in a subgaleal plane to include the supraauricular branch of the occipital artery and the superficial temporal artery. The lower incision began at the level of the outer canthus of the eye and extended above the brows. The upper incision started several centimeters above the supraauricular crease and paralleled the lower incision. A split-thickness skin graft removed from the thigh was applied to the periosteum, fascia and the undersurface of the pedicle of the flap prior to replacing the flap into its original position.

On June 22, 1976 the carcinoma was resected in continuity with a right partial glossectomy, three-quarter mandibulectomy, and a right radical neck dissection. The neck dissection was performed through a modified Schobinger incision with the central limb posterior to the carotid artery and an anterior limb extending into the area of resection. Extreme care was taken to preserve the external carotid artery and at least one hypoglossal nerve. To provide for an adequate margin of resection, 2 cm of normal mucosa and bone were removed with the tumor.

Reconstruction was initiated by bending a heavy gauge Kirschner wire to the normal mandibular contour (Fig. 1). One end of the wire was driven with a mallet through the mandibular marrow cavity into the outer cortex. The other end of the wire was seated into a drill hole in the mastoid tip.

The forehead flap was released from the forehead and brought through a stab incision lateral to the zygoma through the upper cheek into the mouth (Fig. 2). The flap was advanced upon itself to provide bulk to the tongue, and then fashioned into an anterior sulcus and covering for the inner surface of the wire. The flap was sutured to the tongue

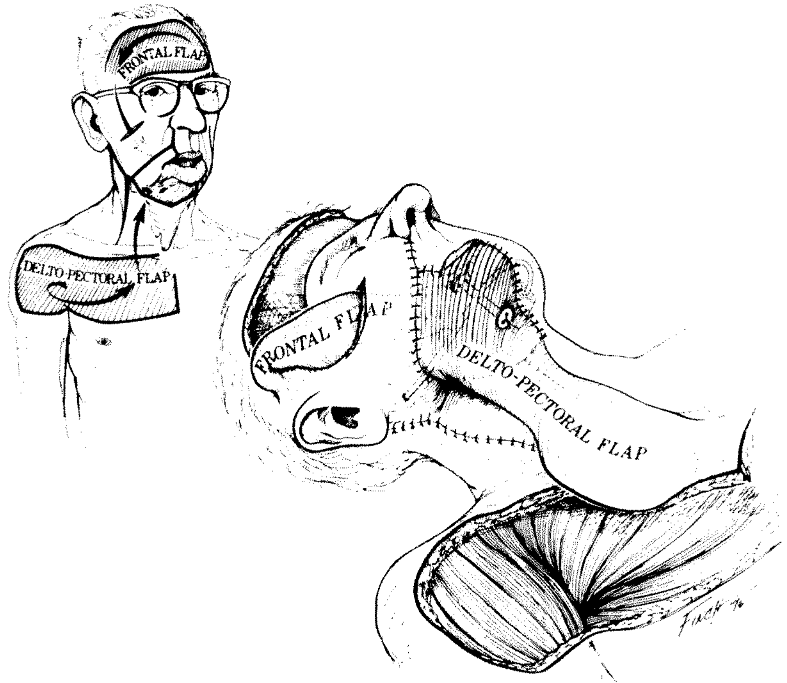

Fig. 2. Reconstruction of the oral-labial sulcus with silastic buttons.

remnant and buccal mucosa with a No. 00 chromic catgut, and an oral sulcus was created with buttons placed on the oral portion of the forehead flap and under the reconstructed chin area (Fig. 2).

The previously delayed deltopectoral flap was released and transposed over the wire to the edge of the forehead flap. The pedicle of the deltopectoral flap was tubed and the lower section sutured to the lower portion of the cervical facial defect. Hemovac drains were employed to prevent hematoma formation and a mild pressure dressing was applied to support the flaps. A tracheostomy was performed and a nasogastric tube inserted for postoperative support.

At four weeks following surgery, the deltopectoral and forehead flaps were released. Excess tissue from the chest flap was discarded while the pedicle of the forehead flap was used to reconstitute an appropriate hairline.

The postoperative course was complicated at one week following surgery by a transient pseudomonas sepsis from a urinary tract infection. Decannulation was achieved in the early postoperative period and the patient gradually regained function of his reconstructed mouth and jaw. With the aid of speech therapy, he was able to develop intelligible speech and was able to swallow some liquids and soft foods. He could not, however, sustain an adequate caloric intake, and to maintain his body weight, a feeding gastrostromy was performed.

The patient was discharged from the hospital seven weeks following surgery and lived the remainder of his days in a nursing home. During this period, his spirits were quite good and he even made plans for the future. His death came five months after surgery from complications resulting from a spontaneous jejunal perforation. Postmortem examination revealed minimal progression of the chest lesion and no evidence of recurrent local disease. The appearance of the patient prior to surgery and three months postoperatively is shown in Figure 3.

DISCUSSION

The combined flap-wire technique appears to be extremely useful in correcting large defects of the oral cavity in which an immediate reconstruction of the mandible, cheek, floor of the mouth, and tongue is required. The methods resemble the formation of a sandwich and the technique has been described with this term.[28] The soft tissues supplied by the combined deltopectoral-forehead flap are essential for support of the cheek and chin, and are necessary to cover the Kirschner wire. As the flaps heal and the tissues soften, the tongue remnants are able to move the flap tissues; the bulk of the reconstructed areas assists in the swallow maneuvers and speech formation. These advantages cannot be achieved with local or split-thickness grafts.

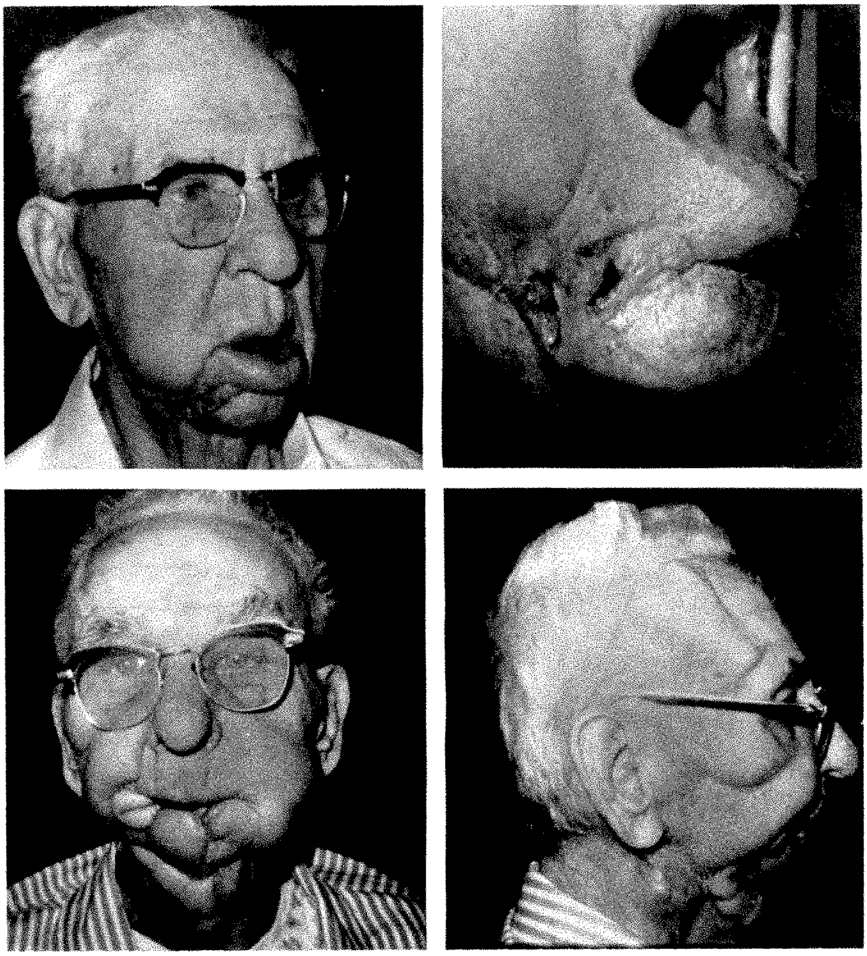

Fig. 3. Pre- and postoperative photographs of combined flap-wire techniques.

The viability of these flaps is well-known from general usage and is further enhanced by "delay" procedures. Regional flaps transfer well-vascularized, nonirradiated tissues into an area for reconstruction, an advantage not equaled by irradiated local and cervical flaps. The increased viability aids in preventing fistula formation and offers further carotid protection.

Wire reconstruction of the mandible is an essential part of the sandwich technique. The Kirschner wire provides a skeleton for facial contour and support for stabilization of the flaps and upward motion of the larynx during swallowing. The approximation of normal physiologic motion prevents aspiration, and thus extensive mandibular resection can be carried out without a need for laryngectomy.[19]

Complications have been noted from various reconstructive techniques used in forming the flap-wire composite, but none of these sequelae have been major problems. Facial nerve paralysis can occur with transfer of the forehead flap lateral to the zygoma, but rarely is this a permanent injury. Hair on the intraoral portion of the flap can also be an annoyance, but this can be avoided by removing the hair-bearing portion during the delay procedure. Poor skin color matches and scarring of the forehead from split thickness skin grafts are minor problems that can be corrected at a later date. Fistula formation is a possibility, but with healthy, delayed, well-vascularized flaps it is unlikely to occur. Minor fistulas can be controlled during the immediate postoperative period by application of occlusal dressings and proper care.

SUMMARY

A combined flap-wire technique is described for immediate reconstruction of large defects resulting from tumor resection of the oral cavity, mandible and facial-cervical skin. The method consists of a forehead flap to repair the intraoral defects, a thick gauge Kirschner wire to stabilize the mandible, and a deltopectoral flap to repair the cutaneous defect. The major advantage of the technique is to provide immediate cosmetic and functional reconstruction using healthy regional tissues.

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SURGICAL TREATMENT OF CONGENITAL CHOANAL ATRESIA

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OSLO, NORWAY

SUMMARY — In a follow-up, 2 to 27 years postoperatively, of 43 patients with unilateral choanal atresia a high frequency of relapses was observed. In 47% of the cases, preoperative symptoms had reappeared, and in 84% scar tissue had reduced the choanal opening to less than half of normal size. In most of the patients a transpalatinal approach was used, either ad modum Ruddy, Wilson or Owens. In order to improve the results, the surgical method and the postoperative treatment were changed in a new series of 15 patients with unilateral atresia. These patients, 6 to 26 years of age, were operated on by a transpalatinal approach during two months in the autumn of 1974. After removal of the atresia, the posterior part of the nasal cavity was modeled, with a dental drill, to increasing diameter towards epipharynx. To keep the opening patent a PVC tube was left in the choana for six weeks postoperatively. The results were encouraging. Two and a half years after the operation there were no relapses.

Choanal atresia is an inborn occlusion of the choanal opening (Fig. 1) resulting in continuous nasal discharge, impaired sense of smell and restricted nasal respiration. In the newborn with bilateral affection, death from aspiration and asphyxia is a potential danger. The diagnosis is based on clinical and x-ray examinations and the treatment is surgical. Several types of operations are at hand in the management of this disorder, differing mainly in the way of obtaining access to the choanal area: 1) transpalatinal approach;[1-5] 2) transnasal approach;[6-9] 3) transanthral approach;[10,11] and 4) transseptal approach.[12,13]

A reexamination, 2 to 27 years postoperatively of 43 patients with unilateral atresia (Group A) treated in the National Hospital of Norway, Oslo, revealed that 47% of the cases still had symptoms indicating a narrow or reoccluded choana. In 84% of the patients, the opening of the operated choana was reduced to a size less than half of the other normal side. The age of the patients at the time of operation did not influence these results. The frequency of relapse in patients operated on in early childhood (two to four years old) nearly equalized the frequency of relapse in patients operated on between 4 to 6 years, 6 to 8 years, 8 to 10 years, 10 to 14 years of age, or later in life.

Most of these patients were operated on by a transpalatinal approach (two transnasally) without any modeling of the nasal walls, although 61% had a funnel shaped nasal cavity revealed by x-ray examination before the operation. In 95%, the occlusion was total, bony in 75% of the cases. After the operation a tube was left in the choana for *14 days*, at maximum.

The results obtained were not satisfactory, probably due to the surgical method employed, the postoperative

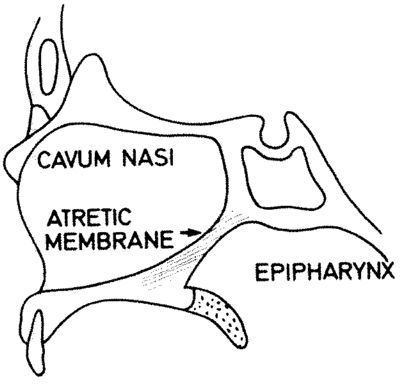

Fig. 1. Location of occluding wall in choanal atresia.

From the Department of Oto-rhino-laryngology, National Hospital of Norway, Oslo 1, Norway.

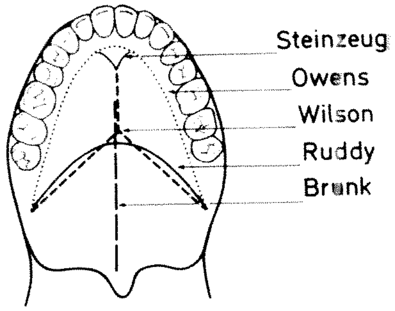

Fig. 2. Palatal incision.

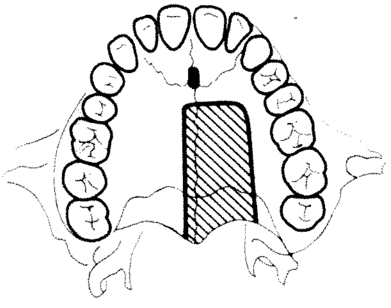

Fig. 3. Resected part of the hard palate.

treatment or both. The *aim* of this investigation, therefore, was to find out, in a new series of patients, if the results could be improved by changing the surgical method and the postoperative treatment.

MATERIAL AND METHODS

Material. The material consists of 15 patients, 6 to 26 years old, with total unilateral choanal atresia operated on during two months in the autumn of 1974 (Group B). Eight of these patients (Group B_1) had their first operation, while seven (Group B_2) were relapses after previous treatments. In nine patients, i.e., 60%, the nasal cavity was funnel shaped, narrowed towards the atresia (Table 1).

Operation Method. All patients were operated on, in general anesthesia, by the transpalatinal approach. This consists of a palatal horseshoe incision (Owens[3]), followed by elevation of the corresponding mucoperiosteal flap which contains both arteriae palatinae (Fig. 2). The hard palate on the occluded side, plus the nearest 3-4 mm of the opposite side, was removed to some distance in front of the atresia. Through this opening the nasal cavity and epipharynx were accessible (Fig. 3).

Hinged mucosal flaps from both sides of the occluding wall were developed and the wall itself removed. The nasal cavity was then modeled, with a dental drill, to the *largest possible size with increasing diameter toward the epipharynx.* The wall between the nasal cavity and maxillary sinus, and the pterygopalatinal fossa was made paper-thin, especially upwards laterally (Fig. 4). After dressing the wound in the choanal region with the hinged mucosal flaps, a PVC tube of 1-1.5 cm in diameter was placed in the opening (Fig. 4). This tube which passed from the epipharynx (well behind the choana) to the outside of the nostril, keeping the flaps in position, was secured by a stitch through the columella. The palatal incision was then closed.

TABLE 1. PRESENTATION OF MATERIAL (GROUP B) (N = 15 PATIENTS)

	B_1 (5 M, 3 F)	B_2 (5 M, 2 F)
I. Op	8.9 yr	4.9 yr
II. Op		17.9 yr
F. C.	5	7

M - Male; F - Female; I. Op - First operation, $\bar{x}$ age; II. Op - Second operation, $\bar{x}$ age; F. C. - No. of patients with funnel shaped nasal cavity.

Postoperative Treatment. The nasal tube was left in place for *six weeks* postoperatively, and the patients daily treated with 3 million IU of phenoxymethylpenicillin during this period. Reexaminations were made at 3 months, 9 months and 2½ years postoperatively.

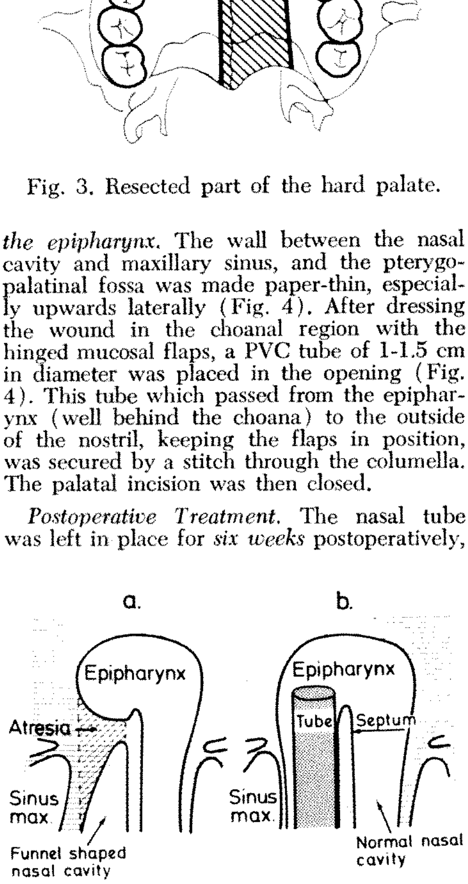

Fig. 4. Horizontal section of the nasal cavities, a) before, and b) after modeling of the lateral nasal wall.

Evaluation of Postoperative Results. As in group A, relapse was defined as a reduction of the operated choana to less than half of normal size. This was judged by posterior rhinoscopy performed in pethinal-diazepam IV analgesia when necessary. Because a more minute specification of the amount of scar tissue was desirable, a reduction to three fourths of normal size was also registered. In addition, reappearance of preoperative symptoms, and lack of well-defined dewing on a mirror in front of the nostrils were recorded.

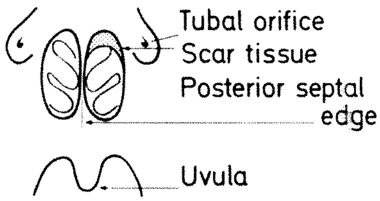

Fig. 5. Location of scar tissue in choanal opening.

RESULTS

After *three months*, in all patients but two, the operated choana was of normal size. In these two patients the tube had by accident been removed on the 14th day, and the choana was completely occluded. A reoperation with a careful repetition of the nasal wall modeling was then immediately performed.

After *nine months*, the size of the operated choana equalized that of the unoperated, normal side in 11 patients, but in the remaining four there had been a reduction to a little less than three fourths of normal size with a scar brim upwards laterally (Fig. 5). All had an open nose with no reappearance of preoperative symptoms.

After *2½ years*, the results were nearly unchanged from the nine months observation. One of the patients did not meet for reexamination but in the remaining 14, the condition appeared to be consolidated.

DISCUSSION

The problems concerning this disorder, including description of different surgical methods, have been dealt with in a large number of papers.[9,14-23] Comparisons, however, are difficult to make, partly because the criteria of relapse are vaguely defined, partly because strict statements of observation periods are missing. In addition, the amount and location of postoperatively formed scar tissue, giving a grading of the postoperative results, have not been discussed. Thus the statements of Hogeman and Toremalm[24] still seem to be valid: "In none of the mentioned papers, however, have the functional and morphological postoperative conditions been followed up." This situation, the apparent lack of parallel studies, leaves for comparison only the results observed in the two groups (A and B) of the present paper.

From the case-sheets and the reexamination of *Group A* (former mode of treatment) it emerged that the condition was constant from about one year postoperatively. Concerning *Group B* (new treatment) the relapses were recorded during the first nine months after the operation. From the ninth month to the 2½ years observation the results were almost unchanged. Two and a half years postoperatively the condition appeared to be consolidated and the results obtained in Groups A and B should therefore, despite the different duration of observation periods, be comparable.

As suggested by others[2,17,22,25] *a prophylactic antibiotic* was administrated during the period of after-treatment. The transnasal tube, acting as a foreign body close to the wound surfaces in the choanal area, may possibly induce infection. This should be avoided, partly because of the vicinity of the brain, partly because granulation tissue, induced by infection, augments cicatrization. In the present study, all patients were daily treated with 3 million IU of phenoxymethylpenicillin. Postoperative infections did not appear.

The patient's *age* at the time of operation is of importance, but *not* primarily in regard to a successful treatment of the atresia. Other considerations, however, have to be dealt with. The transpalatinal approach includes a removal of the posterior two thirds of the median palatal suture (Fig. 3). A destruction of this growth zone during childhood has been shown to reduce by significance the transversal maxillary growth.[26] The growth in this suture is in harmony with the growth trends of the individual, large in early childhood, completed after puberty. A postponement of the operation to late childhood or youth is therefore advisable. To avoid respiratory distress, by bilateral atresia during the two to three first weeks neonatally, a patent airway can be secured by applying a simple mouth-tube or a "McGovern nipple."[27]

Concerning the influence on maxillary transversal growth, caused by the operation, this can be avoided by using the transnasal technique. This method, however, gives a poor view of the operation field, and the two transnasally operated patients in Group A both relapsed. As regards the transseptal method, this constantly demands later plastic corrections on the external nose[12] and is therefore more comprehensive than the simple transpalatinal operation. The transantral approach has, according to the literature, been performed only in a few cases,[10,11] and comparisons to this method are therefore difficult.

The transpalatinal technique is simple, gives easy access to the choanal area and makes the modeling of the upper-lateral nasal wall easy to perform.

This *widening of the nasal cavity* is based on three concepts. *First*, an increasing diameter of the nasal cavity in the posterior direction is, according to McGovern and Fitz-Hugh[28] of importance to the normal transnasal air passage. *Second*, a funnel- shaped nasal cavity, also described by other authors[2,6,10,29,30] was present in more than 60% of the cases. *Third,* the upper lateral part of the choana should be particularly enlarged in order to reduce the effect of cicatricial shrinkage. Some scar tissue always appeared in this place (Fig. 5). In Group A, widening of the nasal cavity's posterior part was not performed.

Mucoperiosteal flaps were developed to cover the wounds in the choanal area and to reduce the formation of scar tissue. A plain extirpation of the atresia and modeling of the nasal cavity together with an indwelling tube, might suffice in this concern. In the treatment of tracheal-stenosis, Montgomery[31,32] and Ilberg[33] report good results of long-term intubation with silicon rubber tubes without the use of mucosal flaps.

As proposed by other authors[3,19,24] and supported by the results of this investigation, the *after-treatment* (transnasal tubing) should be of long duration (here six weeks). In Group A, no patient had retained the transchoanal tube for more than 14 days. In Group B, relapses recorded at the three-months observation appeared when the tubes were removed on the 14th day postoperatively. In other situations, for instance in the treatment of tracheal stenosis,[31-33] and in the management of mucoceles in the frontal sinus with reconstruction of the nasofrontal duct,[34,35] a long-time intubation is recommended, i.e., more than four weeks. In the present investigation a PVC tube was used. A silicon rubber tube may be even better, because this material is softer and more inert.

Whether the changed surgical method or the prolonged postoperative treatment is the most important concerning the results achieved, is not indicated by this investigation. The relapses, however, were significantly reduced. Reappearance of preoperative symptoms was reduced from 47% to zero, and the frequency of cases having an operated choana less than half of normal size was reduced from 84% to zero. Only three patients, i.e., 22%, had developed scar tissue reducing the choana to three fourths of normal size, but all had an open nose with a satisfactory air passage.

Used as their own controls (one normal side), only patients with unilateral affection were included in this investigation, but of course, the method described is also applicable in patients with bilateral choanal atresia.

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SIZE OF BONY LABYRINTH OF HUMAN INFANT AND ADULT COMPARED TO THAT IN CERTAIN ANIMALS

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SUMMARY — Comparative anatomic studies of the bony labyrinths of humans and those of a full grown pony, zebra, grizzly bear, seal and domestic cow were performed. Fusible metal was injected into the labyrinths and the resultant casts were then measured. The similarities and differences were noted and discussed.

In recent years, teaching in all branches of medicine has changed a great deal. This applies to many of the basic sciences, including anatomy. Although dissection is of prime importance, movies and other audiovisual methods have helped our knowledge considerably.

The anatomy of the temporal bone has been carefully studied grossly and microscopically but little attention has been given to the making of corrosion casts of the bone itself. By means of fusible metal, the whole of the bone or part, such as the bony labyrinth, can be injected, leaving the rest of the bone intact. The method of injecting the temporal bone has been decribed elsewhere.[1] The melted material used in the preparation of these specimens, known as Wood's metal, is a mixture of lead, cadmium and tin.

In order to compare the size of the bony labyrinth of the human newborn infant and adult to that of certain animals, it was considered necessary to take a series of measurements from a number of infants and a similar number of adult casts and note the average of the two groups.

Quoting from an article comparing "The Bony Labyrinth of the Newborn Infant and of the Adult," written many years ago, the author[2] summarized the findings as follows:

"1. The bony labyrinth of the newborn infant is practically the same size as that of the adult.

2. There is a slight increase in size in some of the measurements, owing to growth, which is most marked in the semicircular canals.

3. The increase in length of the canals is greatest in the external, less in the posterior, and least in the superior canal.

4. The posterior semicircular canal is the longest and the external canal the shortest in both the new-born infant and the adult.

5. The diameter of the posterior canal itself at the vertex is the greatest, and that of the superior canal the least.

6. A small cochlea may be associated with large canals or a large cochlea with small canals.

7. The semicircular canals in the human are not regularly curved but show at times definite angles, which are sometimes well seen in the posterior canal.

8. Finally, the plane of each of the three canals is not the same throughout its course. Each canal seems to be twisted on its axis, this condition being most marked in the superior canal."

In the previous study,[2] a comparison was made between various parts of the bony labyrinth, the length of the canals and the size of the cochlea. The average measurements of six casts of infants were compared to those of six adults. For instance, the extreme length

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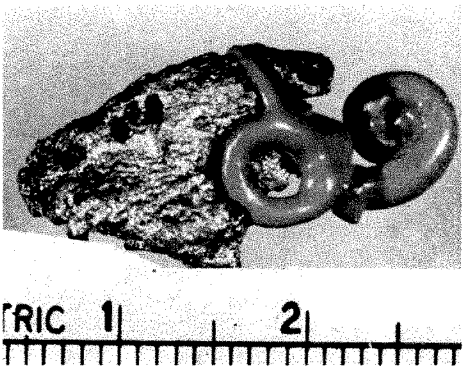

Fig. 1. Cast of left bony labyrinth of a human fetus of eight months shortly before birth. The solid mass on the left shows the extent and cellular distribution of even the dense petrous portion of the temporal bone. Unfortunately, this view hides the left external canal. Note that measurement is in centimeters.

of the labyrinth from the vertex of the posterior canal to the innermost part of the cochlea was 18.50 mm in the infants and 18.46 in the adults in this series.

A few temporal bones of premature infants were obtained and injected with fusible metal. One 8½-month fetus had a total length of 16 mm and another of eight months a length of 14 mm (Figs. 1, 2).

Shortly after these casts were completed we made a trip to Great Britain. During our stay in England we were invited by a couple of old friends, Sir Victor and Lady Negus, to have dinner with them one night at the London Zoo in Regents' Park.* Later in the evening we were taken through the reptile house where we were fortunate indeed to meet the curator of the Zoo. Having explained my interest in the temporal bone, he very graciously looked around and found four dried skulls of animals that I was able to bring home.

These consisted of a fully-grown pony, zebra, grizzly bear and a seal. The skull of a domestic cow was also obtained from a local abattoir and the inner ear injected with fusible metal.

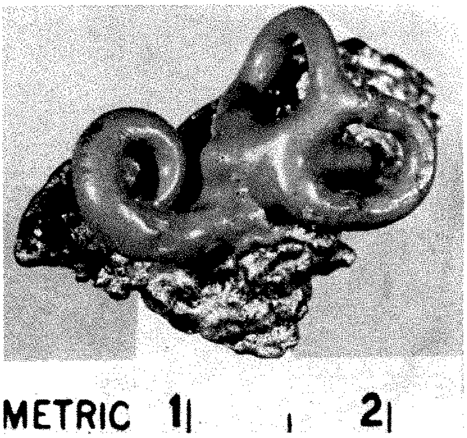

Fig. 2. Cast of a right bony labyrinth of a six-months-old human infant, the same size as that found in the adult.

Apart from the size of the human bony labyrinth, as compared to the animals mentioned, there were some minor differences in the shape of the canals and the number of turns in the cochlea. For instance, the canals in the human were not as regularly curved as those in the animal skulls examined. Also, all the standard textbooks mention that the spiral tube of the human cochlea has 2½ turns around its central axis or modiolus. In contrast, in the animals mentioned, the cochlea had slightly less than 2½ turns and, in fact, the cochlea of the seal had only 2¼ turns – this in spite of the fact that the cochlea was larger than in any of the other specimens (Table 1).

In comparing the size of the labyrinths of the animal skulls to the human, they were found to be very much smaller than one would expect. For instance, in the pony the external length from the outermost point on the vertex of the posterior canal to the innermost point on the lowest whorl of the cochlea was 18 mm – almost identical with that found in the human infant at birth and also in the adult.

The canals of the pony and the horse are rounded and regularly curved. This also applied to a fully grown zebra

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*Through his close association with the London Zoo, Sir Victor Negus had a wealth of material at his disposal in his study of the larynx. His careful observations formed the basis of his two classic volumes on the comparative study of the larynx in animals. Many of the illustrations were drawn by his wife Eve, who is an accomplished artist.

TABLE 1. SIZE OF BONY LABYRINTH IN HUMANS AND ANIMALS

	Turns in Cochlea	*Length of Labyrinth*	*Weight (kg)*
Human adult	2½	18	68
Human infant	2½	18	2.7
Grizzly bear	Slightly less than 2½	20	454
Zebra	Slightly less than 2½	18	136
Seal	2¼	22	295
Pony	Slightly less than 2½	18	113
Cow	Slightly less than 2½	18	454

(Fig. 3) which weighs roughly 136 kg. Each canal lies in the same plane without any lateral twist such as is found in some animals. The plane of the horizontal canal is low in the pony and the superior canal is tilted backwards in contrast to some other mammals and humans. The cochlea is definitely of the flat type which is generally found in hoofed animals.

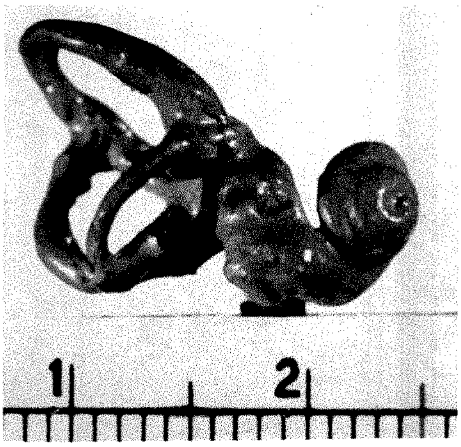

Fig. 3. Right inner ear cast of a mature zebra almost identical in size with that of a cow.

The bony labyrinth of the cow is again small when one thinks of an animal weighing perhaps 454 kg. In the specimen examined it measured 18 mm in the extreme length from the outermost point on the vertex of the posterior canal to the innermost point on the lowest whorl of the cochlea. Also in the cow, at least in the cast examined, the posterior canal was found to be the largest and the horizontal the smallest. The canals are well-rounded and throughout their course lie in one plane without any lateral deviations. The superior canal is slanted backwards similar to that noted in the pony. The cochlea has slightly less than 2½ turns.

The bony labyrinth of a large, fully grown grizzly bear is quite interesting (Fig. 4). Compared to the zebra and cow, the bony canals and cochlea were very small for such a large animal. On questioning the curator at the London Zoo, he stated that the skull was that of a bear that weighed at least 454 to 545 kg. Surprisingly, the measurements were only slightly larger than those of a human infant and adult. The extreme length from the outermost point on the vertex of the posterior canal to the innermost point on the lowest whorl of

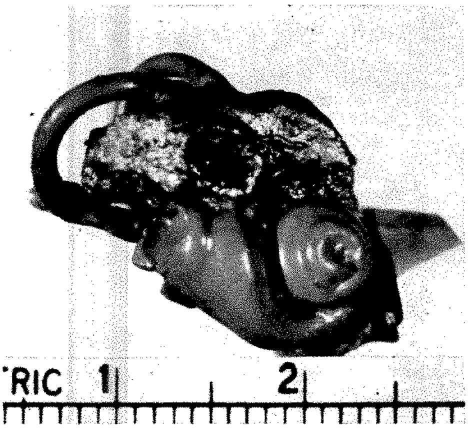

Fig. 4. Cast of right bony labyrinth of a fully grown grizzly bear showing a large first turn of the cochlea.

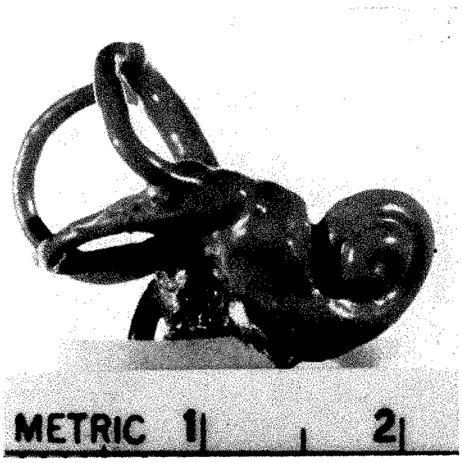

Fig. 5. Metallic cast of the right inner ear of an adult harp seal, the largest of the specimens examined.

the cochlea was 20 mm, only 2 mm longer than in the cow. The canals were exactly the same size as those found in the cow.

The bony labyrinth of a mature common seal (Fig. 5) is of special interest because it was the largest of any of the species examined. This seemed unusual as the animal weighed in the neighborhood of 295 kg according to the curator. The total length of the inner ear measured 22.0 mm in its greatest length from the outermost point on the vertex of the posterior canal to the innermost point on the lowest whorl of the cochlea. The diameter of the lowest whorl of the cochlea was 5.5 mm and that of the second whorl 3 mm. This was almost double the size of the same measurements found in the pony and cow. The bony labyrinth of the seal was larger than any of those examined, in spite of the fact that the cochlea had only 2¼ turns as compared to 2½ turns in the human. Although the posterior canal is the most regularly curved of the three, it is not as symmetrical as in many other animals.

DISCUSSION

The extreme length of the bony labyrinth of the human infant at birth and the adult as well was about 18 mm, almost identical to that found in the pony, zebra and cow. This seems strange when we think of a newborn baby weighing 2.7-3.15 kg, a human adult perhaps 68 kg, a pony 113 kg, a zebra 136 kg, and a cow 454 kg.

The human cochlea, both in the infant and adult, has 2½ turns according to the standard textbooks. All the animal casts examined showed slightly less than 2½ turns. In contrast, the seal with a body weight very much less than some of the other mammals, had a cochlea with only 2¼ turns, in spite of the bony labyrinth being by far the largest. One thinks of most animals as having very acute hearing but perhaps the total range is not as great as in humans.

Regarding the canals themselves, a number of points might be mentioned. Their size and diameter are not uniform; as in humans, some show definite angles, others lie in the same plane throughout their course, while some appear twisted on their axes.

One striking difference in the size of the canals might be mentioned. In the human, the posterior canal is the longest and the external canal the shortest. This rule does not hold true for all mammals. For instance, in the seal the superior canal is easily the longest and the posterior canal the shortest.

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ADDENDUM

During the preparation of the article an amusing sidelight might be mentioned. On describing the material for this paper to a prominent otologist, he showed considerable enthusiasm but added that it would be of interest to compare the bony labyrinth of a whale and a fully grown elephant. When the skulls of the zebra, pony, grizzly bear and seal were obtained, I considered myself lucky, although it was necessary to procure an extra suitcase to bring them home. On arrival in Canada, the Customs officer had to pick the bag for inspection which contained the animal skulls. Perhaps it was heavier than the ones with our personal belongings. Needless to say he was surprised and shocked when he saw the skulls packed carefully together. Luckily I had a note from the curator on official letterhead paper saying that he had given them to me for experimental purposes. I can only imagine his reaction if the Customs man opening a bag had found the skull of a whale and an elephant.

Acknowledgment — This article would not be complete without a word of appreciation to Lady Negus and the late Sir Victor for their help in this venture. Lacking their cooperation, it would have been impossible to obtain the animal skulls which were so necessary in the preparation of this paper.

Reprints — Dr. Tremble died on July 7, 1977. Requests for reprints should be sent to J. D. Baxter, MD, Department of Otolaryngology, Royal Victoria Hospital, Montreal, Canada.

OTOLARYNGIC PATHOLOGY TRAINING PROGRAM

A training program on otolaryngic pathology, presented by the Armed Forces Institute of Pathology (AFIP) in conjunction with the Committee on Otolaryngic Pathology, AAOO, is currently being offered at the Department of Otolaryngic Pathology, AFIP. The course covers both temporal bone pathology as well as surgical pathology of the head and neck area.

Requirements are flexible but preference is given to residents and practitioners in Otolaryngology and Pathology, both military and civilian, who wish to expand their knowledge of ENT pathology. The course, for which there is no charge, is designed to be given quarterly, beginning in January, April, July and October; however, consideration will be given to those seeking shorter training periods.

Requests for course applications should be directed to: The Director, Armed Forces Institute of Pathology, ATTN: AFIP-EDZ, Washington, DC 20306.

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SYNOVIAL SARCOMA OF THE HYPOPHARYNX

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SUMMARY — Primary synovial sarcoma of the hypopharynx is an extremely rare neoplasm. Only 16 cases could be traced in the literature so far. An additional case, in a 29-year-old male patient, is presented. Progressive disturbance of deglutition and speech, choking sensation, and mild respiratory distress were his original complaints. Our case differs from those previously reported in that a) the tumor was pedunculated, and the site of its attachment could be very well-defined, and b) unusual intratumoral destructive hemorrhage turned the case into an emergency. The pedicle was radically excised together with part of the grossly uninvolved underlying tissue, and the tumor was removed in toto. The histological findings are described. The patient is under observation. No recurrence has been noticed 11 months after surgery, and there are no signs of metastasis. The origin of the tumor and its treatment are discussed.

Synovial sarcomas are rather uncommon highly malignant neoplasms of mesenchymal origin, and in most cases are confined to the extremities.[1-3] The hypopharynx is a very unusual and rare primary anatomic site. Cadman et al[4] in their review of 134 cases of synovial sarcomas treated in the Mayo Clinic between 1905 and 1960, found only one case originating in the neck. We were able to trace in the available literature 49 cases of synovial sarcoma of the head and neck regions reported so far.[4-28] Sixteen of them originated in the hypopharynx.[7,9,13,17,20,23,27,28] An additional case is reported herein.

Synovial sarcoma of the hypopharynx appears to be a slow growing tumor, characterized by the high incidence of local recurrences. It is highly malignant, and gives lung metastasis by vascular route. Young individuals are usually affected.[9,13,17,20,21,27,28]

CASE REPORT

A 29-year-old male patient was initially examined at the ENT outpatient clinic of the Hadassah University Hospital, Jerusalem, in September 1976, for a 3-months' history of progressive disturbance of deglutition and speech, choking sensation and mild upper respiratory distress. The latter was usually manifest on exertion or when the patient was lying on the left side. On indirect laryngoscopy, a mobile, pedunculated, oval-shaped, reddish tumor, measuring about 2x3 cm in diameter, was visible in the right piriform recess. It was attached to the anterolateral pharyngeal wall and partially obstructed the inlet to the larynx. On palpation, the tumor was smooth, firm, and mobile. The epiglottis was free. A tomographic study of the larynx and hypopharynx confirmed the findings. No neck masses or cervical lymphadenopathy were noted at examination.

With a tentative diagnosis of fibroma of the right hypopharynx, the patient was referred for an elective excision of the tumor. He did not, however, appear at the scheduled date.

Six weeks later the patient was delivered to the emergency ward because of an acute hemorrhage from the throat. He reported that at the beginning of the bleeding he had expectorated a portion of the tumor which he brought with him in a handkerchief and showed to us. The bleeding stopped spontaneously, but disturbances of speech and deglutition noticeably increased. At indirect laryngoscopy, the tumor appeared hemorrhagic and larger in size than at the first examination, though part of it had undergone necrosis following intratumoral hemorrhage, and was expectorated. There still were no enlarged cervical lymph nodes. The general physical examination did not reveal any pathological findings. Liver scan was normal, bone survey and x-ray examination of the chest were negative.

On the following day, a direct hypopharyngoscopy was performed under general anesthesia with nasotracheal intubation. An oval pedunculated tumor, measuring 3 cm in maximum diameter, and attached to the right pharyngoepiglottic fold, was filling the right

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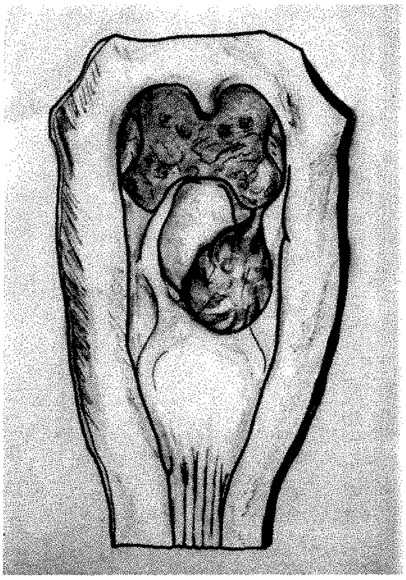

Fig. 1. Drawing of the synovial sarcoma (in black) of the hypopharynx as viewed posteriorly.

piriform fossa and partly blocking the laryngeal inlet (Fig. 1).

After the pedicle was radically excised together with part of its attachment to the pharyngoepiglottic fold, the tumor was removed in toto. There was no bleeding either during or after the operation.

The postoperative course was uneventful, and all pathological symptoms disappeared.

At the time of preparation of this report 11 months have elapsed since the excision of the tumor. The patient has not received radiotherapy and is in good general condition. Neither local recurrence nor enlarged lymph nodes in the neck have been detected, and repeated chest x-ray examination has not shown any sign of pulmonary metastasis. A biopsy taken from the site of the origin of the tumor three months after surgery, proved to be negative. The patient is under observation and undergoes routine hypopharyngoscopy once a month.

PATHOLOGICAL FINDINGS

The surgical specimen consisted of several pieces of soft hemorrhagic tissue, the largest measuring 2 cm in diameter (it had been sectioned after removal). On histological examination the tissue was found to consist of two kinds of cells: fusiform cells with a pale eosinophilic cytoplasm and moderately pleomorphic nuclei with occasional mitotic figures. These cells showed parallel arrangement in "streams" (Fig. 2) and formed the spindle cell component or "phase" of the tumor.

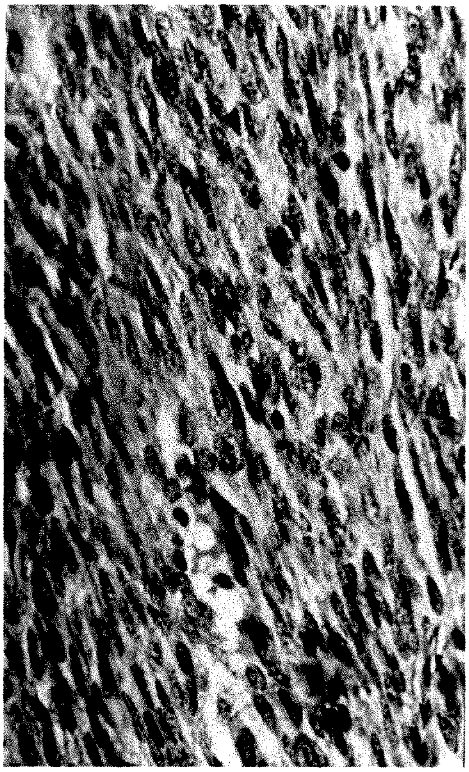

Fig. 2. Spindle cell "phase" of the tumor. The cells are arrayed in parallel rows forming oriented streams. Nuclear pleomorphism is mild to moderate (H & E, X 400).

The second type were plumper cells with oval eosinophilic cytoplasm and rather large, slightly pleomorphic, nuclei. These epithelioid cells showed marked tendency to arrange themselves into tubular or pseudoglandular structures (Fig. 3) sharply delimited at their periphery by fine strands of connective tissue. These constituted the second "epithelial" phase of the tumor. Their lumen often contained a dense mucoid material rich in acid mucopolisaccharides, as shown by its strong positivity with the colloidal iron stain. The material was hyaluronidase sensitive. In some areas the second phase of the tumor took the form of rather wide spaces lined by cuboidal epithelium-like cells. A papillary projection, with a fibrovascular stalk and a surface lining by the same cuboidal cells would oc-

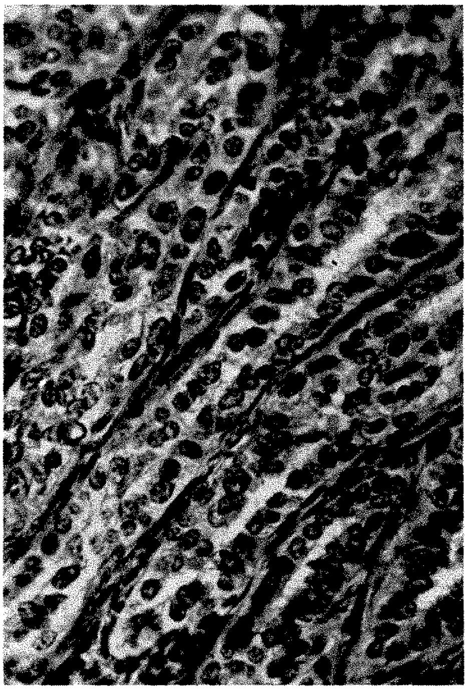

Fig. 3. Epithelioid "phase" of the tumor. The cells are plumper, oval, and line well delimited tubular or pseudoglandular structures. Nuclear pleomorphism is somewhat more prominent (H & E, X 400).

casionally be seen in the lumen of such spaces. The tumor, though strictly speaking not encapsulated, was rather sharply delimited at its periphery by a narrow band of apparently compressed connective tissue, covered by a layer of squamous epithelium. At one end the tumor bordered on striated muscle tissue which appeared not to be invaded by neoplasia; however, a massive destructive hematoma in this very area made a definite decision on invasion or noninvasion impossible.

The histological diagnosis was biphasic synovial sarcoma.*

DISCUSSION

Two aspects of synovial sarcoma of the hypopharynx should, we believe, be touched upon: the origin of the tumor and its treatment.

The relationship of synovial sarcomas to anatomic synovial structures is often tenuous or nonexistent.[4] They not uncommonly arise at sites which have no apparent relation to the synovium of a joint capsule, to a bursa, or to a tendon sheath. Jernström[13] was the first to suggest that the neoplastic cells may derive from synovioblastic differentiation of connective tissue. Roth et al,[28] in an analysis of 24 cases of synovial sarcoma of the head and neck, suggested that the site of origin of the tumor might be the cervical prevertebral tissue. In our case such an assumption would be irrelevant because of the obviously anterior localization of the tumor in the hypopharynx and absence of any evident link to the posterior pharyngeal wall. We would rather tend to look for the source of the synovioblastic tissue in the bursae of the anterior wall of the larynx and pharynx, such as the infrahyoid and retrohyoid bursae, or in the ligaments and membranes of this area, such as the hyoepiglottic and the cricopharyngeal ligaments and the thyrohyoid membrane.

It should also be noted that our case differs from those previously reported in the literature in that a) the tumor was pedunculated, and the site of its attachment could be very well-defined, and b) the unusual intratumoral destructive hemorrhage turned into an emergency.

As for the treatment of synovial sarcomas of the head and neck, the method of choice is early radical excision of the primary tumor.[24,28] Surgery is usually extensive[3,6,9,11,14,17,28] and associated with a radical neck dissection if there is lymph node metastasis.[1,16,17] Many authors[5,6,8,10,16,17,24,28] usually add a course of radiotherapy before and/or after surgical procedure. This is based on encouraging reports of increased survival rates in patients with synovial sarcomas who underwent combined therapy, despite the general consensus that soft tissue sarcomas are radio-resistant. Lately it has been suggested[9,29] that adjuvant systemic chemotherapy with doxorubicin (Adriamycin®) may increase the survival rate in synovial sarcomas.

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*Because of the extreme rarity of this kind of neoplasm in the hypopharynx, slides were sent for consultation to Dr. F. M. Enzinger at the Armed Forces Institute of Pathology, Washington, D.C. Dr. Enzinger kindly examined the slides and was in full agreement with our diagnosis (personal communication).

In the presented case, however, extensive surgery seemed to us unnecessary, since it might have caused the patient more harm than good. The pedicle of the tumor, as previously mentioned, was very well-defined at its attachment to the pharyngoepiglottic fold, and was excised together with a part of the grossly uninvolved underlying tissue. Histologically the tumor was well-differentiated and with a prominent epithelioid component indicating the possibility of a slightly better prognosis. The patient has been under strict observation since the operation, and is being checked once a month. Three months after surgery a biopsy was taken from the site of origin of the tumor and proved to be negative. There was no cervical lymphadenopathy. It was, therefore, decided to refrain from radiotherapy, too, at this stage. Eleven months have now elapsed since excision and the patient is clinically free of tumor, and there are no signs of metastasis either local or distant. Extensive surgery and/or radiation combined with systemic chemotherapy would be contemplated, should the tumor recur or should cervical metastasis appear.

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HEMANGIOMA OF THE NASAL BONES: RADIOGRAPHIC APPEARANCE

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ANDREW GANZ, MD BERNARD TAWFIK, MD

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SUMMARY — Four additional cases of hemangioma involving the nasal bones are presented, bringing the reported cases to 15. The radiographic findings of nasal bone hemangioma are distinctive, permitting easy diagnosis. Hemangioma involving the nasal bones may result in a reticular or "soap bubble" osteoporosis, spiculation, bone thickening, or a channelled appearance of the nasal bone. Treatment is by local excision.

Hemangioma of the nasal bones is a rare tumor. Only 11 cases are reported.[1-9] This is a benign slowly-growing vascular tumor within the nasal bone with or without involvement of the nasal mucosa, submucosa, subcutaneous tissue, or skin.

Hemangioma of the nasal bones has a characteristic radiographic appearance which permits easy radiographic diagnosis. Four additional cases of hemangioma involving the nasal bones are presented, bringing the number of reported cases to 15. Its pathognomic radiologic signs and diagnosis are emphasized.

CASE REPORTS

Nasal bone hemangiomas have been observed in four patients since 1971. There were two males and two females of ages 42, 43, 46, and 52.

Three of the four patients presented with similar histories of a slowly-enlarging, painless, hard mass involving the nasal bone. There was no history of nasal trauma, epistaxis, or nasal obstruction. The fourth patient was a 42-year-old female who had a 20-year history of severe recurrent epistaxis with right-sided nasal obstruction.

On physical examination, a hard painless mass involving the nasal bone was found in three of four patients. Average size of the lesion was 2 by 2 cm. The overlying skin appeared normal and was freely mobile. Intranasal examination revealed submucosal extension of the nasal bone mass in one instance. In the other two patients, the intranasal examination was normal. The patient who experienced severe epistaxis was found to have a pulsatile mass involving the nasal bone, anterior septum, and nasal vestibule with lateral displacement of the right nasal bone. The overlying skin was telangiectatic.

The radiographic appearance of the nasal bone suggested the possibility of hemangioma in all cases. The radiographic appearances may show osteoporosis with radiolucent channeling of the nasal bone or a reticular "soap bubble" texture. There may be thickening and spiculation of the nasal bone (Figs. 1-3). Arteriography was performed in the patient with severe epistaxis and revealed feeding vessels from the facial and internal maxillary arteries.

Treatment was complete surgical excision utilizing a lateral rhinotomy in all four cases. A margin of normal bone was included in the specimen. In addition, the facial and internal maxillary arteries were ligated in the patient with severe epistaxis. No episode of excess bleeding was encountered.

Pathologic diagnosis in the four cases was cavernous hemangioma.

From the Departments of Radiology, Otolaryngology, and Tumor Service, Manhattan Eye, Ear and Throat Hospital, New York, New York.

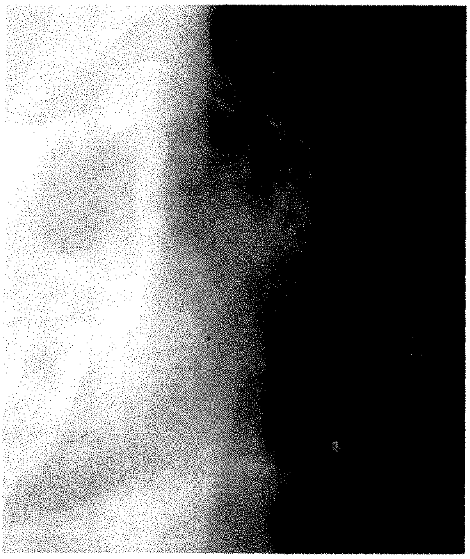

Fig. 1. Lateral view of nasal bones. The right nasal bone has the appearance of termite-infested wood with diffuse areas of osteoporosis. Hemangiomatous involvement of the nasal bone is suggested.

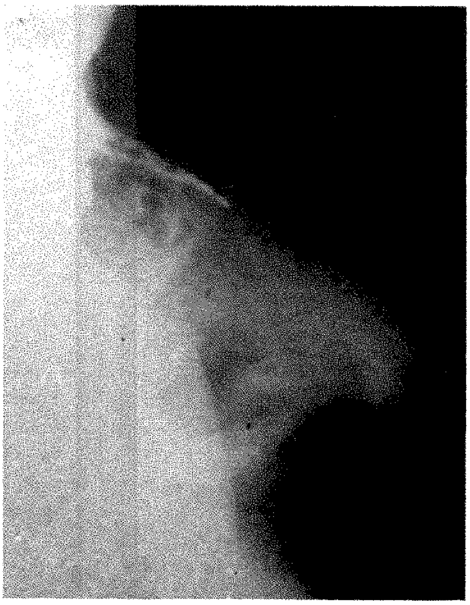

Fig. 2. Lateral view of nasal bones. The radiolucent channeling of the right nasal bone by hemangiomatous vessels suggests the presence of hemangioma.

No postoperative complications were encountered. There have been no recurrences after one to six-year follow-up periods.

No significant postoperative cosmetic deformity resulted in the patients with hemangioma limited to the nasal bone or with limited submucosal intranasal extension. Resection of the hemangioma involving the nasal bone, anterior septum, and nasal vestibule was followed by staged reconstruction of the cartilaginous nasal framework.

DISCUSSION

Clinical hemangioma of bone most frequently involves the vertebral column and skull, with about equal frequency. Asymptomatic small hemangiomas were found in 10.7% of vertebrae studied at autopsy.[7] Radiographic features of vertebral hemangioma show parallel thickened vertical lineal trabeculations. These are distinct and deviate from a normal trabecular pattern. The outer cortical margins are intact. These findings are best seen on lateral views. A "honeycombed" appearance is occasionally seen.

Lesions of the skull exhibit single areas of rarefaction usually extending beyond the normal confines of the skull. The inner table remains intact while the outer table shows erosion. Tangential or profile views show fine striae or reticulations radiating from a common center producing a "honeycombed" or "sunburst" appearance.[7]

Hemangioma arising in other parts of the skeletal system are rare. Only 11 instances of nasal bone hemangiomata are reported in the world literature. The four cases of this report increase the number to 15. Females are affected more than males in the proportion of nine to six. This ratio is similar to hemangioma of other sites.[10,11]

The etiology of nasal bone hemangioma is not known. It has been suggested that it really is a congenital hamartoma manifesting itself as a hemangioma.[11] This theory becomes questionable since all patients have been over 30 years of age except for one patient of 14. Trauma has been implicated as a precipitating factor in 6 of the 15 cases.[2,5,7,9,10] However, in 50% of the cases (the pres-

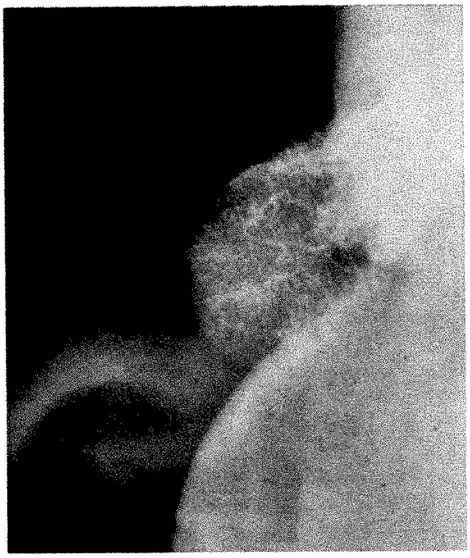

Fig. 3. Lateral view of nasal bones. The reticular, soap-bubble texture and thickening of the left nasal bone indicate hemangiomatous involvement.

ent four cases included), specific traumatic episodes have not been established. Traumatic etiology has not been proved.

Clinically, the majority of patients presented with a hard mass involving the nasal bones. The mass may or may not be tender. Nasal obstruction or epistaxis did not occur in 14 of the 15 cases. In the one case with severe epistaxis, there was extensive submucosal growth of the hemangioma. Nasal bone involvement with limited submucosal intranasal extension has been reported by Bloom. He noted an intranasal mass with intact mucosa.[2] This was also observed in one patient of this report.

Gross pathologic examination of hemangioma of the nasal bones shows a spongy pink to purple-brown mass. The periostium where no intranasal expansion has occurred is intact. Hemangiomatous expansion thins, frays, and destroys the periosteum.[12] Histologically, all nasal bone hemangiomata have been of the cavernous variety with a single layer of normal endothelium. The remaining bony architecture is trabecular with the intratrabecular spaces channelled by hemangioma. There are areas of osteoclastic and osteoblastic activity within the involved nasal bone.[12] The hemangioma of bone not only destroys bone but also induces new bone formation. This results in bone thickening, osteoporosis, spicule formation and a honeycombed, reticular "soap bubble," or sunburst radiographic appearance.

The radiographic appearance of nasal bone hemangioma must be differentiated from several other diseases. Differential diagnosis includes primary and metastatic osteolytic malignancies, phase one of Paget's disease (osteoporosis circumscripta), fibrous dysplasia, histiocytosis, and osteomyelitis. All the above lesions have differentiating clinical presentations and radiographic signs.

The treatment of nasal bone hemangioma is surgical. Most authors advocate local excision, including a small margin of normal bone. Bleeding is usually not severe at surgery. In the limited nasal bone hemangioma, this procedure should not result in significant cosmetic deformity.

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NINCDS NOTES*

CRITERIA ESTABLISHED FOR GUILLAIN-BARRE DIAGNOSIS

Diagnostic criteria for Guillain-Barre syndrome have been established by an Ad Hoc NINCDS Committee. Since Guillain-Barre diagnosis is descriptive, the criteria are expected to help neurologists and non-neurologists recognize the syndrome's diagnostic boundaries.

Drafting of the guidelines was precipitated in part by the increased incidence of Guillain-Barre syndrome last year associated with the swine flu vaccine and by the possibility of an increased incidence this year associated with the newly developed Russian flu vaccine.

A comprehensive report on definition and criteria for diagnosis is available through the NINCDS.

INFANTILE AUTISM

NINCDS is requesting proposals for research on the acquisition of language and communicative skills by speech and sign in infantile autism, (RFP-NIH-NINCDS-78-09).

A study is proposed of the development of communicative skills by autistic children when their language training involves (1) only speech stimuli (2) only sign stimuli (3) speech and sign presented simultaneously, or (4) speech and sign presented independently.

Closing date for proposal receipt tentatively has been set for June 30, 1978. Requests for the RFP package should be sent to: National Institute of Neurological and Communicative Disorders and Stroke, CMB, 7550 Wisconsin Avenue, Federal Bldg., Room 1012, Bethesda, MD 20014. Attn: Mrs. Patricia E. Davis.

PEPTIDE SYMPOSIUM RESCHEDULED

The NINCDS International Symposium on the Role of Peptides in Neuronal Function originally scheduled for September 25-27, 1978, has been rescheduled for May 7-9, 1979. Sessions will highlight: the anatomy and physiology of peptidergic neurons; biochemistry and neurosecretion of peptides; and intercellular peptide communication. There also will be a review of the neurobiology of specific peptides such as angiotensin, neurotensin, LHRH, Substance P, VIP, TRH, olfactory system peptide, bag cell hormone, and neurodepressing hormone.

Symposium organizers are Drs. Jeffrey Barker and Thomas B. Smith of the NINCDS Laboratory of Neurophysiology. Questions concerning the symposium or requests for invitations should be sent to Drs. Barker or Smith, Building 36, Room 2C-02, National Institutes of Health, 9000 Rockville Pike, Bethesda, MD 20014; Tel: (301) 496-2414.

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*This column is prepared monthly by the Office of Scientific and Health Reports, National Institute of Neurological and Communicative Disorders and Stroke. For further information, write or call Carolyn Holstein, NINCDS/OSHR, NIH Bldg., 31, Room 8A-16, Bethesda, MD 20014. (301) 496-5751.

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PERILYMPHATIC OXYGEN TENSION AND VASOACTIVE DRUGS

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SUMMARY — The oxygenation of the perilymph in response to the intravenous injection of vasoactive drugs has been measured in 67 cats using the polarographic method. Of all drugs used, only angiotensin induced a significant raise of perilymphatic PO_2. Histamine, 50% glycerol and 7% Na_2CO_3 reduced the perilymphatic PO_2. Papaverine, furosemid, pyridylcarbinol, naftidrofuryl and low molecular dextran have no significant effect upon the perilymphatic oxygen tension. Rapid changes of systemic blood pressure were found to correlate with subsequent modifications of the oxygen tension in the perilymphatic space.

Many attempts have been made to measure the oxygen tension of the perilymph in order to gain insight into the oxygenation of the inner ear.[1-6] Recent measurements of the oxygen tension in the perilymphatic space according to the polarographic principle by Fisch et al[7] and Murata and Fisch[8] revealed a very close relationship between the PCO_2 of the arterial blood and the oxygen tension of the perilymph in the experimental animal and humans. The aim of the present study was to use the above mentioned polarographic method to investigate the action of vasoactive drugs upon the oxygen tension of the perilymph in cats.

METHODS AND MATERIALS

The method employed for the assessment of the oxygen tension in the perilymph was essentially that described by Murata and Fisch in 1977.[8] Sixty-seven adult cats weighing 2-3 kg were anesthetized with Nembutal® (50 mg/kg). Following tracheotomy the animals were paralyzed with d-Tubocurarine and artificially respirated at a rate of 20-30 breaths per minute. The cephalic vein was cannulated for the administration of drugs. Systemic blood pressure was monitored through the cannulated femoral artery. A Pt and Ag-AgCl electrode with a recessed tip of 100 μ in diameter was placed in the vestibule through the trephinated footplate of the stapes using a micromanipulator. A current voltage convertor with FET operational amplifier (Fig. 1) was used for recording the changes in current produced by different oxygen tensions avoiding thermal changes of the resistor. At the end of the experiments the oxygen electrode was calibrated in saline saturated with nitrogen or with air at body temperature. The blood pressure was determined at one minute intervals after drug injection. No difference in results was seen when perilymph was allowed to flow through the fenestrated footplate or when agar was used to prevent the perilymphatic leakage.

At the beginning of each experiment the responsiveness of the inner ear to inhalation of pure oxygen was checked. The inner ear was regarded as functioning normally when the perilymphatic oxygen tension increased 1.5 to twice the initial value after inhalation of 100% oxygen for 2.5 minutes. Animals which did not demonstrate this response were discarded. The vasoactive drugs (angiotensin, histamine Na_2CO_3, glycerol, papaverine, furosemid, pyridylcarbinol, naftidrofuryl, low molecular dextran) were dissolved in Ringer's solution and injected into the cephalic vein over a five second period. In order to simplify the calculations, the initial value of perilymphatic PO_2 was defined at 100%. The mean absolute value of the perilymphatic oxygen tension was 34.85 ± 1.08 mm Hg.

RESULTS

The effect of the injected vasoactive drugs on the perilymphatic PO_2 was the following:

Angiotensin (Fig. 2). In 10 of 15 cats the intravenous injection of 1μg/kg of angiotensin produced an average increase of perilymphatic oxygen tension of 19.7 ± 8.3% (initial value = 100%). In the remaining five animals no change of the PO_2 was seen. When positive,

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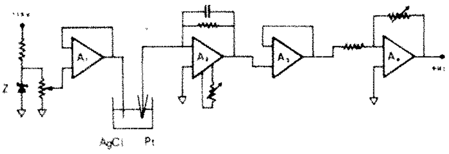

Fig. 1. Schematic diagram of the amplifying system used to record the oxygen tension in the vestibular perilymph. The polarization voltage was produced by A_1. A current voltage convertor with FET operational amplifier (A_2) was used to avoid thermal changes of the resistor when measuring small currents. Z - Zener diode producing a constant voltage of 6.2 v; $A_{1,\ 3\ \text{and}\ 4}$ - Conventional amplifiers.

the response to angiotensin lasted approximately ten minutes and was preceded by a similar increase of the systemic blood pressure of 80.0 ± 33.4 mm Hg.

Histamine (Fig. 3). The effect of intravenous histamine (5 μg/kg) was studied in 14 cats. The perilymphatic PO_2 decreased by an average of 13.3 ± 7.5% (initial value = 100%) for 7-10 minutes in all instances. The change of the systemic blood pressure was of earlier onset, but similar to that of the perilymphatic PO_2. The maximal drop of systemic blood pressure averaged 39.1 ± 10.2 mm Hg.

7% Na_2CO_3 (Fig. 4). The effect of 7% Na_2CO_3 (1.0 ml/kg) was studied in seven cats. The perilymphatic PO_2 decreased by an average of 25.0 ± 11.4% (initial value = 100%) for ten minutes or more in all animals. The systemic blood pressure decreased by an average of 16.7 ± 10.5 mm Hg and usually recovered within ten minutes as well.

50% glycerol (Fig. 5). The effect of 50% glycerol (1.0 ml/kg) was studied in eight cats. The perilymphatic PO_2 decreased by an average of 16.4 ± 8.5% (initial value = 100%) in all animals. The systemic blood pressure showed a significant initial drop of 65.4 ± 5.7 mm Hg followed by a subsequent quick recovery. In five cats the blood pressure returned to normal within ten minutes, while in the remaining three animals a slight hypertension was measured all over the duration of the experiment.

Papaverine (Fig. 7). The effect of papaverine (1 mg/kg) was studied in six cats. The perilymphatic PO_2 dropped within 1-2 minutes only 3.1 ± 3.0% (initial value = 100%) in all instances. The systemic blood pressure was slightly reduced (average value minus 8.7 ± 14.0 mm Hg).

Furosemid (Fig. 7). 0.2 mg/kg furosemid (Lasix®) were administered intravenously to eight cats. A slight reduction in perilymphatic PO_2 of 1.9 ± 4.3% (initial value = 100%) was observed to occur within 2-3 minutes. During the same time there was a minimal increase of the systemic blood pressure

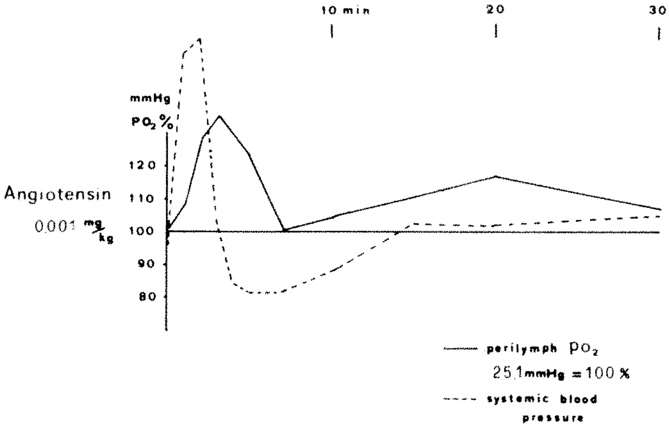

Fig. 2. Effect of intravenous angiotensin upon the perilymphatic oxygen tension. Note that the initial maximal increase in perilymphatic PO_2 was preceded by a similar modification of the systemic blood pressure.

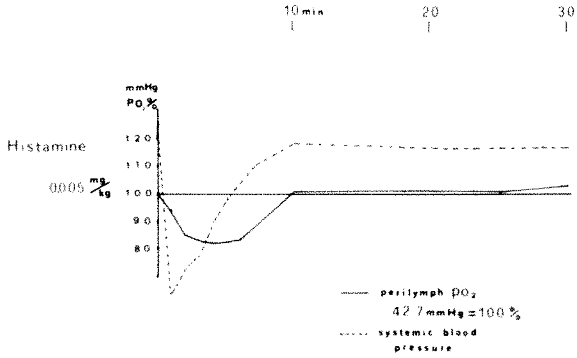

Fig. 3. Effect of histamine upon the perilymphatic oxygen tension. Note the reduction of perilymphatic PO_2 preceded by a similar decrease in systemic blood pressure.

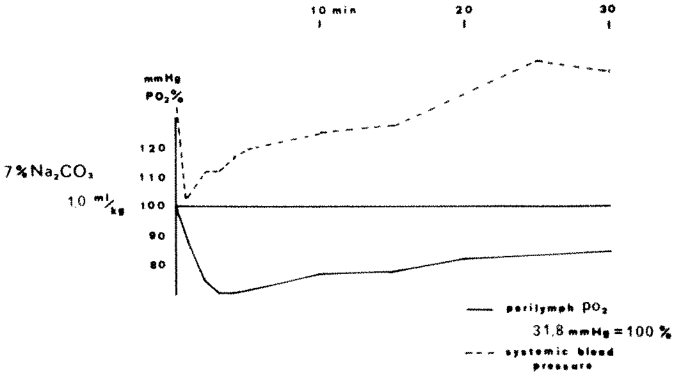

Fig. 4. Effect of 7% Na_2CO_3 upon the perilymphatic oxygen tension. Note the prolonged reduction of perilymphatic PO_2 and the parallel effect upon the systemic blood pressure.

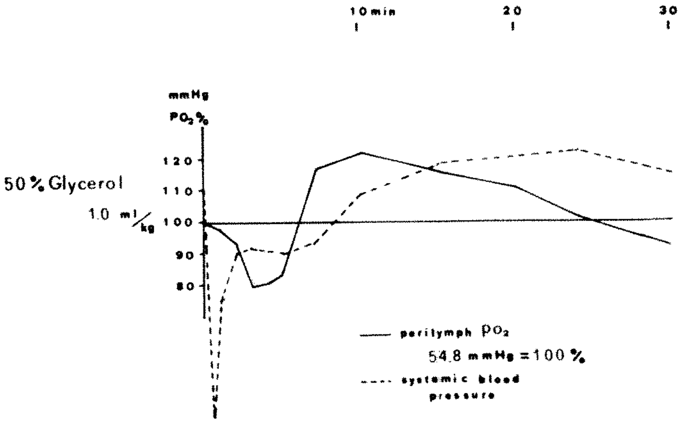

Fig. 5. Effect of 50% glycerol upon the perilymphatic oxygen tension. Note the initial drop in oxygen tension preceded by a similar effect on the systemic blood pressure.

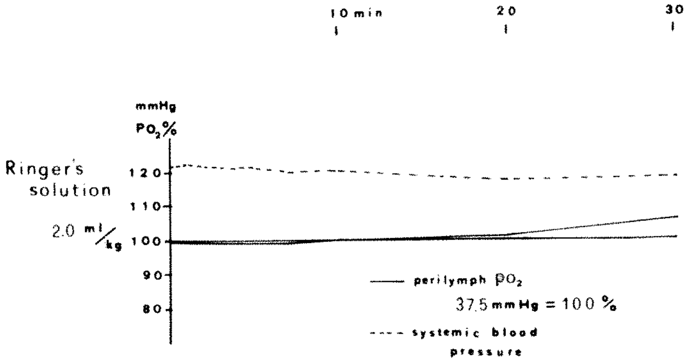

Fig. 6. Effect of Ringer's intravenous solution upon the perilymphatic oxygen tension. Note the minimal reduction of perilymphatic PO_2 in correspondence to a similar modification of the systemic blood pressure.

(average value minus 3.3 ± 0.98 mm Hg).

Pyridylcarbinol (Fig. 7). Following intravenous injection of 5 mg/kg pyridylcarbinol (Ronicol®) the perilymphatic PO_2 of six cats increased 1.5 ± 4.7% (initial value = 100%). Similar minimal changes were recorded for the systemic blood pressure.

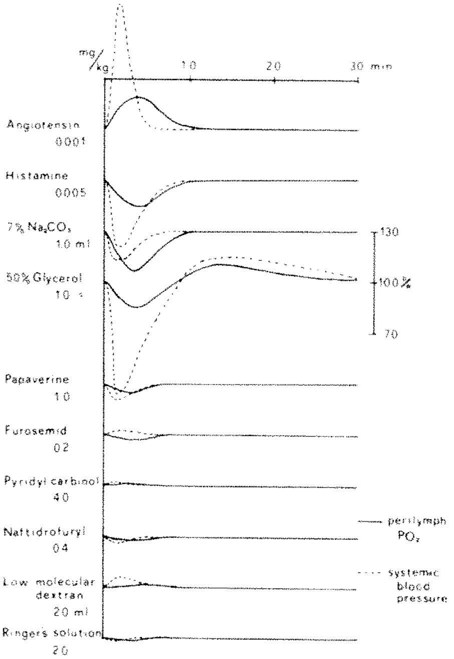

Fig. 7. Average comparative response of the perilymphatic oxygen tension and systemic blood pressure following intravenous injection of various vasoactive drugs.

Naftidrofuryl (Fig. 7). The intravenous injection of naftidrofuryl (Praxilen®) (0.4 mg/kg) produced a slight decrease of perilymphatic PO_2 ($-1.1 \pm 2.9\%$ of the initial value = 100%) in seven cats. There was a slight reduction of the systemic blood pressure (minus 3.9 ± 6.3 mm Hg).

Low molecular dextran (Fig. 7). Intravenous low molecular dextran (Rheomacrodex®) (2 ml/kg) was given to six cats. The perilymphatic PO_2 and the systemic blood pressure increased 1.4 ± 4.5% and respectively 7.0 ± 6.6 mm Hg in all animals.

Ringer's solution (Fig. 6). Ringer's solution (2 ml/kg) was administered intravenously in six cats. A slight drop of the perilymphatic PO_2 and of the systemic blood pressure of 1.5 ± 2.7% and respectively 0.6 ± 4.5 mm Hg were recorded.

DISCUSSION

The effect of the injected vasoactive drugs on the perilymphatic PO_2 is summarized in Figure 7. Angiotensin was the only drug producing a moderate increase of perilymphatic PO_2. Histamine, 7% Na_2CO_3 and 50% glycerol decreased the oxygen concentration in the perilymph. There was no effect on the perilymphatic PO_2 following injection of papaverine, furosemid, pyridylcarbinol, naftidrofuryl and low molecular dextran.

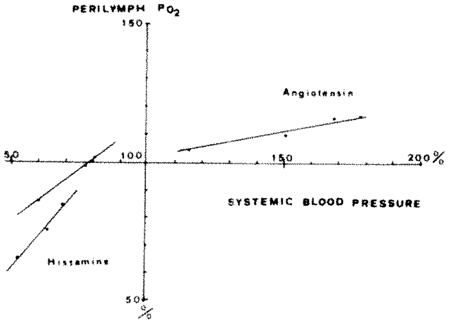

Fig. 8. Regression coefficient curves of systemic blood pressure and perilymphatic PO_2 after administration of angiotensin and histamine. Note that the coefficient of the regression curve determined after intravenous histamine is greater than that following angiotensin. This implies that histamine, next to a strong vasodilating effect, may also modify the permeability of the vessel's wall in the cochlea.

As far as angiotensin is concerned, our results are in agreement with those obtained by Suga and Snow with the electroplethysmographic method in the guinea pig.[9] In contrast to Suga and Snow, who found an increase in cochlear blood flow and a reduction of systemic blood pressure following injection of histamine, papaverine and 7% Na_2CO_3, we have recorded a definite drop in perilymphatic PO_2 preceded by a fall in systemic blood pressure following injection of the same drugs. This discrepancy indicates that the cochlear blood flow cannot be used as a measure of the degree of oxygen diffusion in the perilymphatic space.

The changes observed in the perilymphatic PO_2 following vasoactive drugs indicate that there is a direct correlation between systemic blood pressure and perilymphatic oxygen tension. This relationship is particularly evident following intravenous injection of angiotensin (Fig. 8) and is probably due to both – the increased cochlear blood flow and the changed permeability of the cochlear vessels. The latter effect has been reported to occur in cerebral vessels after a rapid increase in blood pressure and has been related to the opening of tight junctions in the vessel's wall.[2,10,11] The vasodilation produced by histamine may also reduce the systemic blood pressure and alter the permeability of the vessel's wall in the cochlea. This conclusion is supported by the fact that the coefficient of regression measured after injection of histamine is greater than that obtained after angiotensin (Fig. 8).

In contrast to the cochlear blood flow,[9] the perilymphatic PO_2 was reduced following injection of 7% Na_2CO_3 and 50% glycerol. When the drop in perilymphatic PO_2 exceeded 75% of the initial value, the perilymphatic oxygenation remained reduced during the whole observation period of 30 minutes. In view of this fact, which is similar to the one observed by Tsunoo and Perlman[12] after anoxic-anoxia of the inner ear, 7% Na_2CO_3 and 50% glycerol appear to be able to compromise the oxygen transport to the inner ear fluids in a more prolonged and irreversible way than any of the other drugs used. Fifty percent glycerol has a direct osmotic action on the perilymphatic fluids[1] and can also affect the condition of the wall of cerebral vessels according to Rapoport[10] and Tourtellotte et al.[13] The delayed rise of perilymphatic PO_2 and systemic blood pressure, which occurred in three animals following injection of 50% glycerol may be ascribed to the osmotically produced shrinkage of the vascular endothelial cells.

The failure of papaverine, furosemid, pyridylcarbinol, naftidrofuryl, and low molecular dextran in influencing the perilymphatic PO_2 is surprising in view of the widespread clinical use of these drugs. Although the cochlear blood vessels may react differently under normal and pathological circumstances, the obtained results indicate that the action of papaverine, furosemid, pyridylcarbinol, naftidrofuryl and low molecular dextran on the oxygenation of the inner ear still awaits experimental evidence.

In conclusion, the measurements of the perilymphatic oxygen tension obtained according to the polarographic method by introducing a microelectrode through the fenestrated footplate of 67 cats following intravenous injection of various vasoactive drugs has shown that: angiotensin increases, histamine, 50% glycerol and 7% Na_2CO_3 reduce the perilymphatic oxygenation and that papaverine, furosemid, pyridylcarbinol, naftidrofuryl and low molecular dextran have no significant influence on the perilymphatic PO_2.

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QUANTITATIVE EVALUATION OF POSTNATAL BONE GROWTH IN THE AUDITORY OSSICLES OF THE DOG

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SUMMARY — The postnatal bone growth (appositional and internal) in the auditory ossicles and in the tibia of three mongrel dogs was studied by means of tetracycline and alizarin labeling. The appositional growth is characterized by an increase in the external dimensions of the auditory ossicles within the first month of postnatal life. No trace of bone deposition was found after this period of time. The patterns of internal growth are: 1) the rate of primary osteon formation shows the same value in the incus and malleus; 2) these values are always less than those in the primary osteons of the diaphysis of the tibia of the same dog; 3) the time required for the formation of these osteons in the auditory ossicles, like in the other parts of the skeleton, increases significantly with age.

In a previous investigation, Roberto[1] observed that, in the first month of postnatal life, the bone growth of the auditory ossicles of the dog is *qualitatively* similar to that of the other bones of the skeleton. In fact, in that period, the ossicles increase their dimensions by bone deposition on their external surfaces (appositional growth) and their density by bone deposition on the internal surfaces of the primary osteons (internal growth). At the end of the first month, the auditory ossicles have reached their definitive size and density.

The present investigation was undertaken to determine whether osteon growth of the ossicles was also *quantitatively* similar to that of other bones of the skeleton. This was carried out, in dogs, by studying the amount of bone growth (deposition): a) on the external surface (appositional growth), and b) in the primary osteons of the auditory ossicles (internal growth). The results were then compared with those of the tibia. The tibia was selected for several reasons. First, the bone remodeling processes of the tibia of the dog have been described by other authors;[2-5] second, parallels have been drawn between the tibia and ossicles;[1] and third, during the early stages of postnatal life, the tibia is composed, like the auditory ossicles, of primary bone only.

The technique of intravital staining with alizarin and tetracycline was used for this investigation. Mineralizing bone tissue is stained by the administration of these agents and fluoresces red and yellow respectively when examined with ultraviolet (UV) illumination. Consequently, alternate injections of the two agents result in the establishment of fluorescent bands of different colors. The measurement of the thickness of unlabeled bone tissue between two successive fluorescent bands indicates the amount of matrix mineralized during a known period which, of course, is proportional to the velocity of bone growth.

After the initial reports that alizarin red sulphate[6] and tetracycline antibiotics[7] became fixed to the bone matrix during its mineralization, many investigators tried to use this phenomenon to measure the rate of new bone formation. The use of the technique of single or multiple marking, with fluorescent substances, was applied by many authors to study the dynamics of bone deposition in normal and pathological conditions. The following is a cursory review of some of the previous studies. The postnatal bone growth of the ear cap-

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TABLE 1. OSSICULAR BONE GROWTH (INTERNAL) IN THREE DOGS

	Malleus (μm)		*Incus (μm)*		*Tibia (μm)*	
Animal	*A*	*B*	*A*	*B*	*A*	*B*
Dog 1	20.2	9.1	20.2	9.7	31.8	11.2
SD	±1.4	±1.2	±1.0	±1.5	±4.3	±2.2
SE	±0.1	±0.1	±0.1	±0.1	±0.4	±0.3
Dog 2	19.9	8.5	20.0	9.2	35.0	12.0
SD	±1.2	±1.3	±1.2	±1.3	±2.7	±1.9
SE	±0.2	±0.2	±0.2	±0.1	±0.3	±0.3
Dog 3	22.2	10.0	21.5	10.5	32.5	13.0
SD	±1.3	±1.4	±1.3	±1.2	±3.9	±2.6
SE	±0.2	±0.1	±0.2	±0.1	±0.4	±0.4

A - Average thickness of osteonic bone tissue included between the first and second fluorescent band. B - Average thickness of osteonic bone tissue included between second and third fluorescent band. SD - Standard deviation; SE - Standard error.

sule of the rabbit[8] and the bone of the cranial vault of the rabbit[9] and albino rat[10] were qualitatively studied with the use of a single marking in normal animals. The dynamics of osteon formation in the compacta of long bones of almost all the skeleton of the dog[2-4,11] and the cat[12] was studied with the use of multiple marking; the bone growth was then expressed in values of linear velocity of bone formation. Tetracycline and alizarin labeling were also applied in experimental conditions: in dogs with inert bones[5] and under special diet,[13] and in albino rats where the postnatal growth of the cranial bones was studied under hormonal stimulation in comparison to the normal animals.[14]

This technique was applied to several human diseases of bone tissue in order to have a quantitative evaluation of the bone formation in pathological conditions. Particularly studied were acromegaly,[15] osteoporoses,[16] osteogenesis imperfecta,[17] osteomalacia,[18] Paget's disease,[19] bone in hyperparathyroidism,[20] pseudohypoparathyroidism,[21] and hypophosphatemia vitamin D-resistant rickets[22] and otosclerotic stapedes.[23-26] Finally, bones from different parts of the skeleton of normal man were examined.[27-29]

METHODS AND MATERIALS

Three mongrel dogs aged ten days were intraperitoneally injected with tetracycline hydrochloride (Achromycin®) (TRC) and alizarin red sulfate (ARS). The injections were given three times with an interval of 15 days (daily dosage of 20 mg/kg) and the animals were sacrificed seven days after the last administration. The markers were administered in the following way: TRC injected on the 10th and 11th day, ARS on the 27th and 28th day, and TRC on the 44th, 45th, and 46th day. Since the toxic effect of alizarin is well-known, the animals were closely monitored. But all the animals tolerated the dosage of the drug and did not show any significant signs of potential toxic effects.

The auditory ossicles of both sides and the diaphysis of the tibia were embedded in methacrylate and sectioned with an electrical saw* in successive sections of 100 micrometers (μm) thick. Between two successive sections, the bone destroyed by the saw is about 400 μm thick. The malleus was sectioned perpendicularly to the main axis of its various parts, creating three sections of the head, three of the neck, and six of the manubrium. The incus was sectioned perpendicularly to a plane along the main axis of the ossicle, starting from the articular surface of the body. Two sections from the body and two or three from the processes were obtained. The stapes were sectioned across the principal axis permitting a single section in which we see all parts of the ossicle. The sections were ground to a thickness of 40 μm, photographed under UV light on color reversal film (Ektachrome high speed), using a Zeiss Ultraphot II microscope equipped with one or two energizing filters BG 12 and 2 barrier filters OG 50-53, at a standard enlargement of 40x. All the slides were projected to have a final enlargement of 500x. At this magnification, measurements were taken from the maximal fluorescence at the midpoints of the labeled layers, as follows.

To study the amount of the appositional growth, measurements were taken perpendicular to the external surface of the ossicles at 1

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*Gilling Hamco, Braunwill Scientific Co., Rochester, NY.

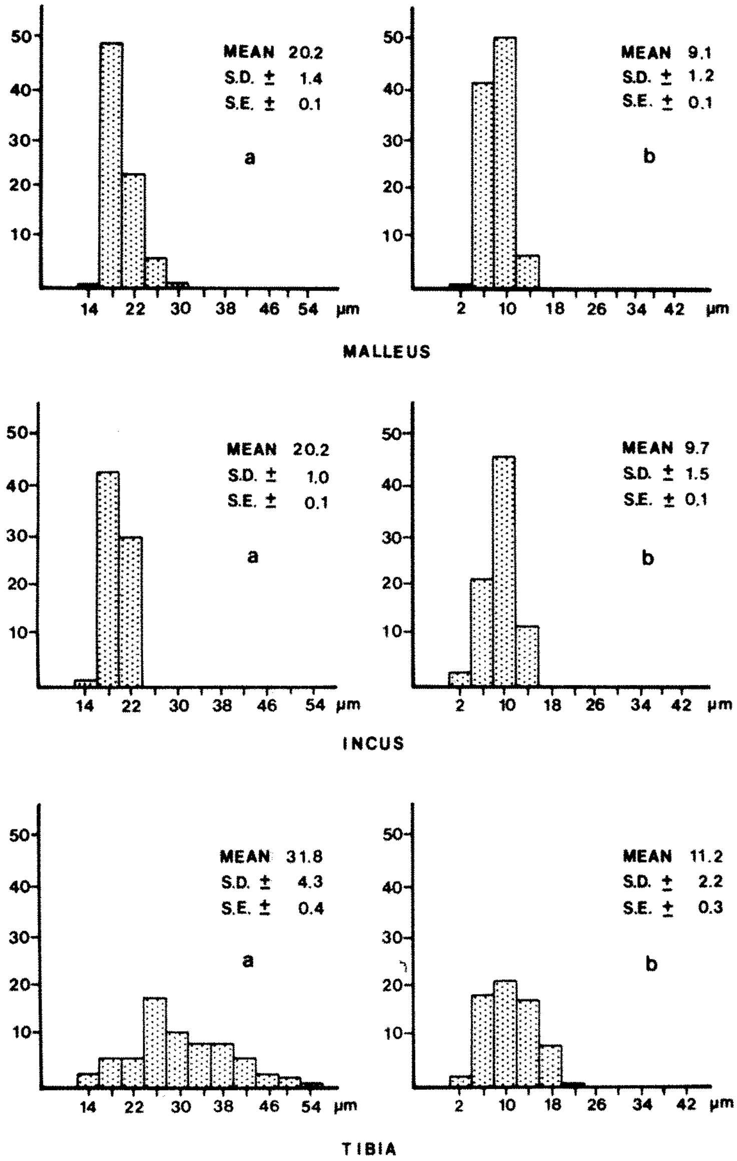

Fig. 1. Internal growth. Histograms showing the average thickness of osteonic bone tissue included between the 1st and 2nd fluorescent band (a) and between the 2nd and 3rd fluorescent band (b) measured in the osteons of the malleus, incus and at the level of the diaphysis of the tibia of the left side of dog. 1. The thickness of bone tissue is expressed in micrometers along the horizontal axis; the number of determinations is reported along the vertical axis. SD - Standard deviation; SE - Standard error.

cm intervals. To study the amount of the internal growth, measurements were taken between the successive labeled rings of the osteons along two (arbitrary) orthogonal diameters when the osteon was sectioned transversally and/or measured perpendicular to the surface every 1 cm when the osteon was sectioned longitudinally. Faint or unclear fluorescent bands were not measured.

RESULTS

The bone growth is expressed in terms of thickness of bone tissue formed during a known period of time (15 days), rather than the daily velocity of bone growth. One could easily divide the thickness of the bone deposition in

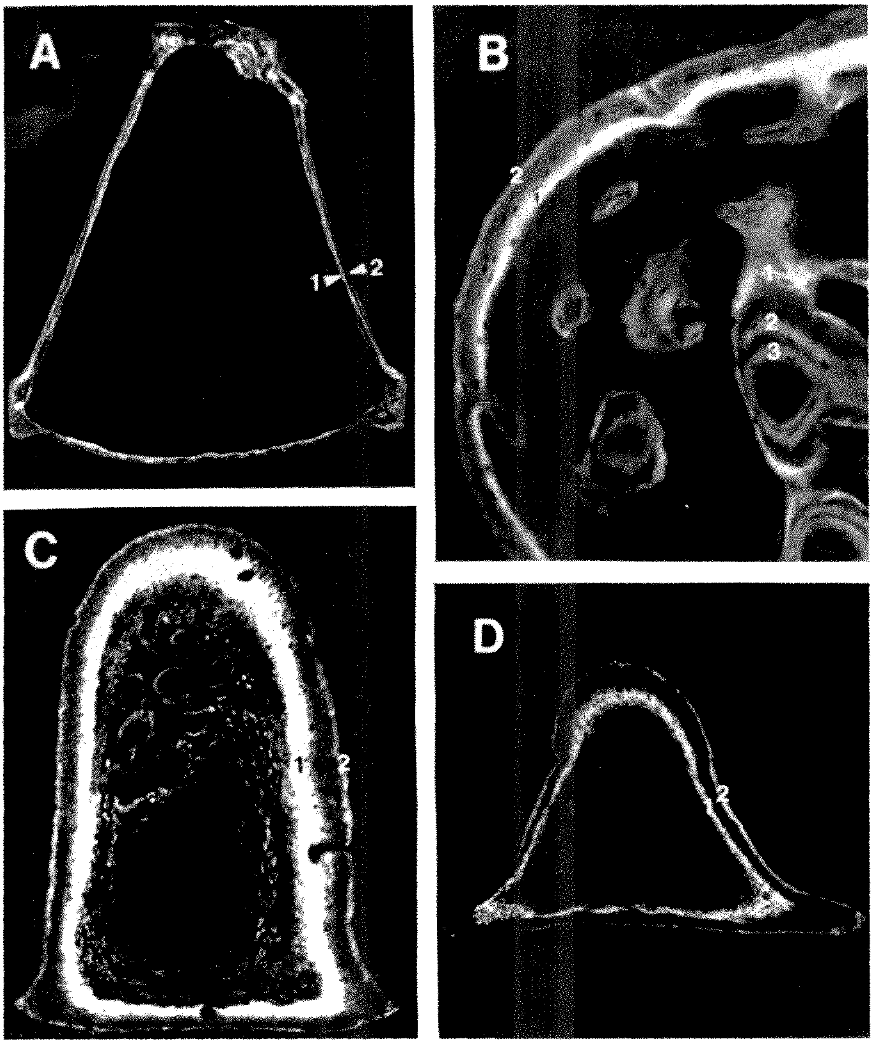

Fig. 2. Appositional growth. Micrographs under UV light of the stapes (A) (X24), incus (B) (X72), proximal half (C) and distal half (D) of the manubrium of the malleus (X54). In black and white photographs one cannot distinguish the different fluorescence of the markers and the autofluorescence of the connective tissue. The numbers 1, 2, 3 indicate the fluorescent bands due to the sequence of the TRC-ARS-TRC administration.

micrometers by the number of days; but in this way one makes the assumption that the bone grows, every day, at a constant velocity. On the contrary, my data show that the thickness of bone deposition, in two identical intervals of time (15 days), varies greatly (Fig. 1 and Table 1). This means that the values of velocity expressed (micrometers of bone formed/number of days) would give misleading values of daily velocity. For this reason I preferred to express my data in terms of amount of bone formation during the period of time examined.

Appositional (External) Growth. In all the ossicles, one or two fluorescent bands were consistently observed (internal and external). The internal (1) fluorescent band corresponds to the first TRC administration and the external (2) band to the ARS administration;

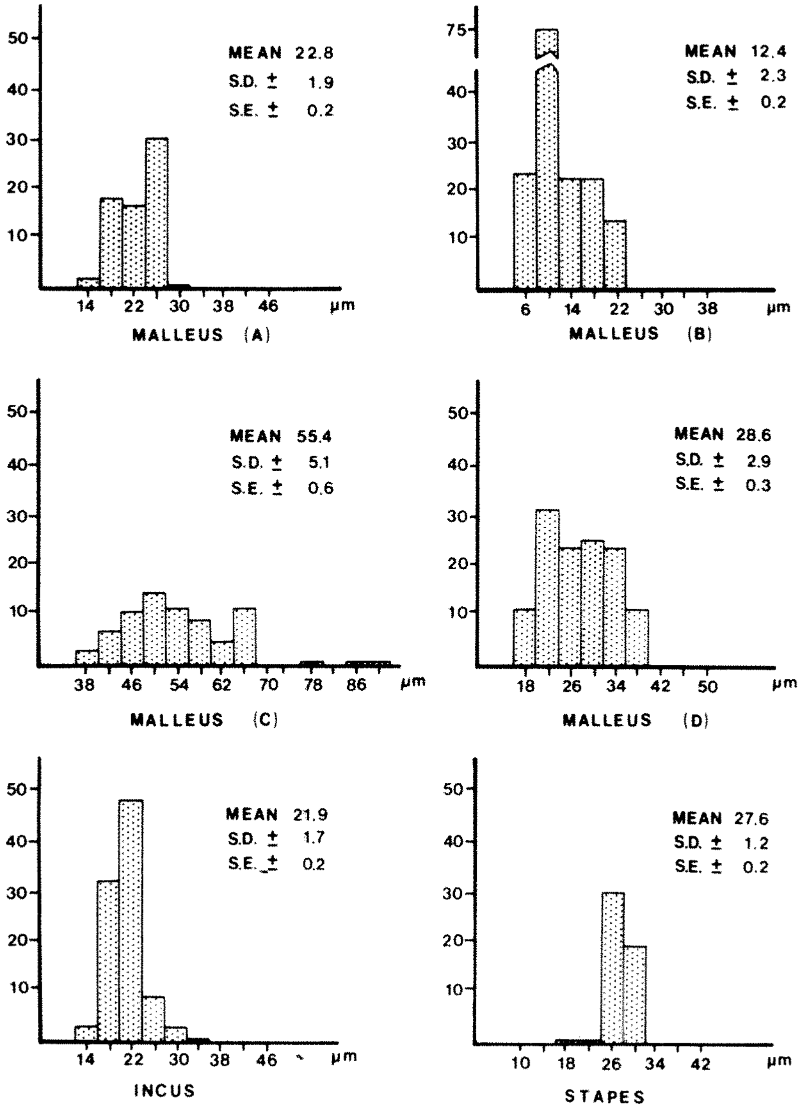

Fig. 3. Appositional growth. Histograms showing the average thickness of periosteal bone tissue between the 1st and 2nd band on the malleus, incus and stapes of the left side of dog 1. The malleus is examined at the level of the head (A), neck (B), proximal half (C) and distal half of the manubrium (D). The thickness of bone tissue is expressed in micrometers along the horizontal axis; the number of determinations is reported along the vertical axis. SD - Standard deviation; SE - Standard error.

the distance between 1 and 2 (Fig. 2A-D) is the bone growth between the 11th and 27th days. A trace of a third fluorescent band at the external surface was never observed (Fig. 2A-D); consequently, there is no appositional growth after 27 days. The unlabeled bone between these two bands shows a substantial difference in thickness in various parts of the ossicles (Fig. 3 and Table 2). In these pictures, the amount of bone laid down on the external surfaces of the ossicles between the 11th and 27th day of life can be seen.

The malleus shows different growth in its various regions (Fig. 3 and Table 2). The head is quite similar to the incus. The neck shows the lowest amount

TABLE 2. OSSICULAR PERIOSTEAL BONE GROWTH (APPOSITIONAL) IN THREE DOGS

	Malleus µm					
Animal	*Head (A)*	*Neck (B)*	*Proximal Half (C)*	*Distal Half (D)*	*Incus µm*	*Stapes µm*
Dog 1	21.5	12.0	54.0	29.5	21.0	28.0
SD	±1.9	±2.3	±5.1	±2.9	±1.7	±1.2
SE	±0.2	±0.2	±0.6	±0.3	±0.2	±0.2
Dog 2	21.5	14.0	50.5	25.0	20.9	25.5
SD	±1.6	±1.9	±4.5	±2.5	±2.0	±1.4
SE	±0.1	±0.2	±0.5	±0.4	±0.3	±0.2
Dog 3	23.5	11.0	51.0	26.5	22.5	26.0
SD	±1.8	±2.0	±3.5	±1.9	±1.6	±1.7
SE	±0.3	±0.3	±0.4	±0.3	±0.3	±0.3

of bone deposition of the other parts of the ossicle. The manubrium shows a great difference when we consider its proximal half and its distal one (Fig. 2C, D); in the former, the rate of bone formation is reduced by about 50% from the proximal part.

Regarding the incus (Fig. 2B), the values shown in Figure 3 and Table 2 concern the body and the short process. The rate of the bone deposition shows minimal differences between these two regions of the ossicles and, for this reason, the values are reported in a single histogram (Fig. 3). No trace of a second fluorescent band is present in the long process; this suggests that, in this part of the incus, the external growth stops earlier than in the other parts.

With regard to the stapes, the values reported in Figure 3 and Table 2 indicate the amount of bone deposition of the crura; the first fluorescent band corresponds to the internal surface of the ossicle and the second fluorescent band corresponds to the external surface (Fig. 2A). The head and footplate are covered by a layer of cartilage and, therefore, do not show any trace of periosteal bone deposition. Figure 3 shows that the thickness of the unlabeled bone between the two fluorescent bands is quite uniform.

Internal (Osteonic) Growth. In the auditory ossicles, the primary osteons frequently show two fluorescent bands and sometimes three (Figs. 2B and 4B). In the first case, the bone deposition occurs during the first two administrations of the markers or the last two. The different fluorescence of the bands permits us to identify clearly the moment and the type of treatment. In the second case, the bone deposition occurs during the administration of all the markers. Osteons with only one fluorescent band were never observed.

Only the incus and malleus were examined because the number of osteons present in these ossicles was sufficiently high to enable us to keep a record. The stapes were excluded as the osteons in all the dogs are few and only present in the head and in the contour of the footplate.

Figure 1 shows that the mean value of the thickness of the *internal area* (included between the second and third fluorescent band) is significantly reduced in comparison with the thickness of the *external area* (included between the first and second fluorescent bands), even if the time between the three administrations of the markers is always the same (15 days). This means that the rate of the bone deposition strongly decreases during the formation of the osteons.

Figure 1 also demonstrates the similarity in the values of the rate of osteonic bone deposition in the incus and malleus when we examine the thickness of the *external* and *internal* area.

Comparing the tibia with the ossicles

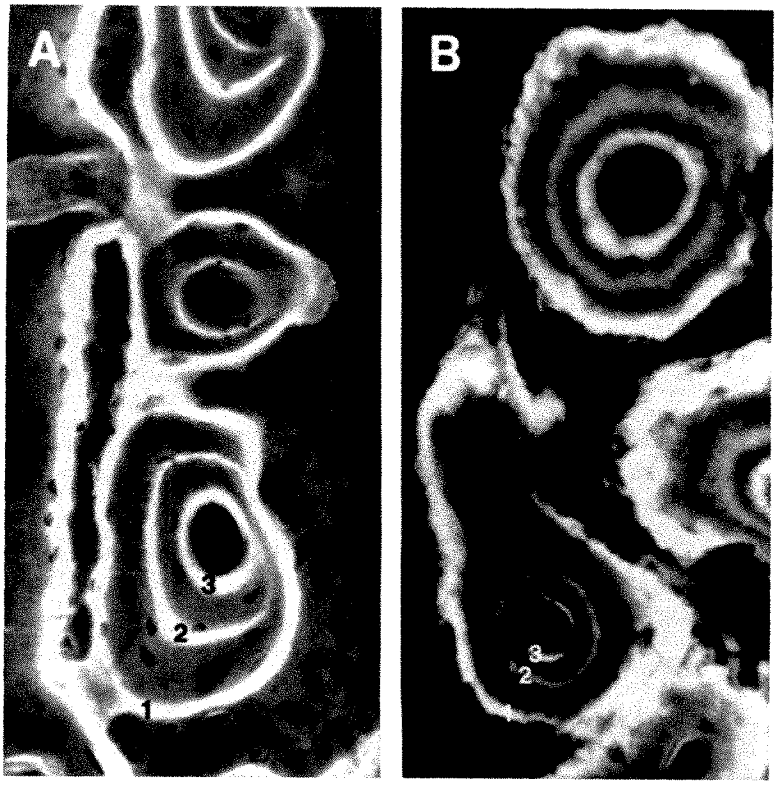

Fig. 4. Internal growth. Micrographs under UV light of primary osteons at the level of the tibia (A) and incus (B) (X210). The picture in A was taken with only one energizing filter to show that the markers label the bone and not the connective tissue. See Fig. 2 for numbers 1, 2, 3.

(Fig. 1 and Table 1), the rate of bone deposition in the former is always higher when the two intervals of time between the treatments of the markers are examined. It could be considered that the difference between the tibia and the ossicles is far more significant during the first interval of the administration of the markers (Fig. 1 and Table 1). To summarize, the primary osteons of the tibia decrease their growth rate more rapidly than those of the auditory ossicles and tend to eliminate this difference as time continues (Fig. 4A, B).

To evaluate Figures 1 and 3, one can see that the standard deviation and standard error show low values. In fact, the thickness of the unlabeled bone included between two successive fluorescent bands shows hardly any change; this means that the rate of bone deposition is rather uniform in the different parts of the ossicles. Besides, the values of appositional and internal growth found in the auditory ossicles and tibia show a quite constant pattern in all three animals examined (Tables 1, 2).

DISCUSSION

Regarding the appositional growth, our data show that the auditory ossicles of the dog increase their external dimensions, by appositional growth, within the first month of postnatal life. No trace of bone deposition was found after this period of time on the external surfaces of these ossicles.

These data are in agreement with our previous research,[1] but are not in accordance with the data presented by Anson and Bast[30-32] in the man, by Hoyte[8] in the rabbit, and by Bateman[33] in the auditory ossicles of the young microphthalmic mutant mouse. In fact, these investigators found that the auditory ossicles reach their definitive size and shape before birth, and that postnatal modifications are insignificant. However, in each of these cases, the ossicles were not studied for the purpose of analyzing postnatal growth.[30-32] On the other hand, areas of "external accretion and erosion"[33] or "actual surface growth"[8] after birth, described by these authors, do not explain the dynamics of the postnatal appositional growth in ossicles. The partial disagreement could be explained by the different animal species studied and/or by the research technique. In fact, the technique of the double or triple marking of bone deposition with fluorescent substances (TRC and ARS) permits us to observe clearly very small traces of bone deposition. The presence of these fluorescent bands of newly formed bone allows us to visualize the bone formation of the various parts of the ossicles while a quantitative evaluation of the distance between the bands allows one to estimate the amount of bone growth in the ossicles.

However, we must consider that the macroscopic external size of the auditory ossicles does not show significant changes during postnatal life, because the increase of the external dimensions is very small and occurs only in the first month after birth. From these data, it could be assumed that the auditory ossicles of man also increase their dimensions in the postnatal life; however, it is difficult to project to the exact period of time when growth of the ossicles is occurring. Care must also be exercised when inferring from an experimental animal to man.

With regard to the internal growth of the osteons, our results indicate that the rate of primary osteon formation is approximately the same in the incus and malleus; moreover, these values are always less than those in the primary osteons of the diaphysis of the tibia in the same dog. This difference is especially evident during the first interval of the administration of the markers. In fact, the internal growth of the osteons of the tibia decrease more rapidly than that of the auditory ossicles and tend to eliminate this difference with time.

It was also found that the time required for primary osteon formation, in the incus and malleus of the dog, increases significantly with age. These data agree with those of Vanderhoeft et al,[2] Lee,[3] Frost et al,[27-28] Sedlin and Frost,[29] Manson and Waters.[12] Using the same technique, these authors observed in the dog, cat and man, that the rate of the bone deposition (growth) decreases with time in the regularly shaped osteons (circular, elliptical). Marotti and Camosso[4] found in the long bones of young and adult dogs the same results studying the whole osteonic population, including regular and irregular systems. More recently, Marotti[5] found the same results even in the secondary osteons of inert bones of dogs in comparison to the contralateral mobile ones. Moreover, studying the spongiosa of the tibia of young and old dogs, it was found[34] that the rate of bone deposition decreases also during the formation of the trabeculae.

All these results indicate that the dynamics of the primary osteon formation of the auditory ossicles of the dog are qualitatively similar to that of secondary osteons of the long bones of the dog, cat and man. In fact, the process of the osteon formation is similar in both types of bone tissue: the rate of bone deposition is very high at the beginning and gradually decreases with time.

A question could be raised about the validity of the measurement technique. On examining the osteons of the auditory ossicles with three markers (Figs. 2B and 4A, B), it can be noted that the thickness of the second fluorescent ring, formed during three days of ARS blood concentration, appears thinner than the internal area of unlabeled bone, formed during the second 15-day interval. This could be explained in two ways. First, the fluorescent red band labeled by ARS is thicker when examined under UV light; in fact, Marotti and Camosso[4] showed that the red fluorescent band actually looks sharper and thinner

(30%) when examined under ordinary light. To avoid this source of error, the distance between the two successive labeled layers was measured from the midpoints of these marks. Second, by the rapid decrement of the rate of bone deposition during the formation of osteonic lamellae; the mean value decreases about 50% when the two intervals of time are examined.

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FIFTH BRITISH ACADEMIC CONFERENCE IN OTOLARYNGOLOGY

The Fifth British Academic Conference in Otolaryngology will be held July 22-27, 1979, at the University of Birmingham (U.K.). Master will be Sir Geoffrey Bateman, MA, FRCS. This conference has academic and scientific programs with distinguished international contributors to discuss a wide range of modern developments within the specialty.

Morning plenary sessions will be held with papers from invited speakers. Open panel discussions will be a significant feature and instructional sessions will also take place as well as audiovisual programs. Finally there will be a scientific and trade exhibition.

For further information and application forms write: V. Hammond, FRCS, 55 Harley Street, London WI, England.

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ESTIMATE OF VITAMIN A IN THE GUINEA PIG COCHLEA

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SUMMARY — Microfluorometric estimates of the membranous structures of the freeze-dried guinea pig cochlea have demonstrated that vitamin A is present in these tissues at a concentration of 21.2 μg/gm (SD ± 4.77 μg) which is approximately ten times the vitamin A concentration in most other tissues.

With the sole exception of hair cells of the inner ear, all special somatic afferent receptor cells have been shown to contain or functionally depend upon vitamin A. Wald[1] and others have investigated the role of vitamin A in visual excitation in the rods of the retina. Bernard et al[2,3] have demonstrated that vitamin A deprivation leads to a gradual loss of normal taste discrimination in rats and a diminished electrical activity of the chorda tympani nerve with NaCl stimulation of the tongue. Duncan and Briggs[4] showed that parenteral vitamin A administration reverses some cases of anosmia. In addition, they found that the olfactory epithelium contained 6.2 μg of vitamin A per gram of tissue.

Vinnikov[5] observed that the origin of structural and functional characteristics of all special sensory cells in vertebrates may be traced to a modified cell provided with motile cilia or flagella and suggested that all of these cells are metabolically associated with vitamin A (Fig. 1).

We designed an experiment to estimate the concentration of vitamin A in the structures of the cochlear labyrinth of the guinea pig using microfluorometric assay techniques. A modification of the micofluorometric technique of Hanson and Warwick[6] was utilized, since ultraviolet absorption and colorimetric methods proved too insensitive for the microgram tissue samples available. We found that a fluorescent compound with the spectral characteristics of vitamin A was present in the guinea pig cochlea at a concentration of 21.2 μg/gm (SD ± 4.77 μg) or approximately ten times the level found in most other tissues (Fig. 2).

Twelve adult guinea pigs were deeply anesthetized with ethyl ether and decapitated. The bullae were removed rapidly and placed into liquid nitrogen. The frozen temporal bones were then placed onto a block of dry ice (solid CO_2) and the lateral bony wall of each cochlea removed using microdissection techniques under a Zeiss operating microscope. Care was taken to leave the structures of the spiral ligament and the frozen scalae in place. The partially dissected cochleas were then freeze dried in a vacuum dessicator for three days.

Each freeze-dried cochlea was then dissected under the operating microscope. Using the cochlear microdissection techniques of Matschinsky and Thalmann,[7] the tissues of the entire cochlear labyrinth (spiral ligament, stria vascularis, organ of Corti, and tectorial membrane) were placed into a specimen vial and weighed on a Mettler analytical balance. The tissues from three cochleas were pooled for each

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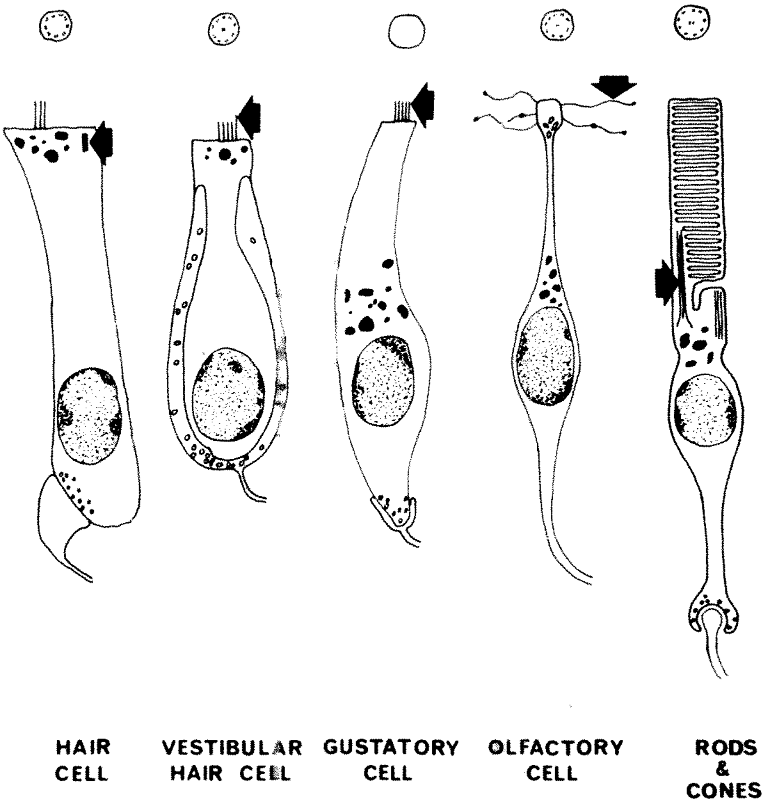

Fig. 1. All mammalian special sensory receptor cells are modified ciliated cells; each is bipolar in configuration and contains a motile cilium or the derivative of a motile cilium (arrows).

sample. The total dry weight of each sample was 300 μg.

Tissue samples were also obtained from the lung. The kidney and liver were obtained at the time of sacrifice, freeze dried and weighed. Serum samples were obtained via a cardiac puncture.

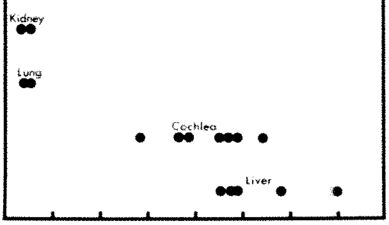

Fig. 2. The concentration of a compound with the spectral characteristics of vitamin A is shown on the abscissa and expressed in micrograms per gram of dry tissue.

Tissue samples were then homogenized in 40% ethyl alcohol and mixed in a Vortex mixer. The samples were extracted with triple distilled *n*-hexane. The organic phase was pipetted into a 1 ml capacity microcuvette. Fluorometry was then performed on a Perkin-Elmer MPF-2A recording fluorescence spectrophotometer using an excitation wavelength of 332 nm, and an emission wavelength of 475 nm and a band width of 10 nm.

A standard fluorescence curve was obtained by dissolving weighed quantities of retinyl acetate (Sigma) in *n*-hexane.[8]

Vitamin A concentration in the tissue samples was calculated from the standard curve and the original weights of each sample or pooled sample. Resultant vitamin A concentrations were then expressed in micrograms per gram of dry tissue.

We found a fluorescent compound with the spectral characteristics of vitamin A in the cochlear tissues at a concentration of 21.2 μg/gm (SD ± 4.77 μg n=24) which is approximately ten times the vitamin A concentration of most other tissues. This substance had an excitation maxima at 332 nm and an emission maxima at 475 nm. The concentration in other tissues was as follows: lung 1.9 μg/gm ± 0.3 μg, kidney 1.9 μg/gm ± 0.1 μg and serum 4.2 μg/gm ± 0.4 μg. The tissue concentration of vitamin A in the inner ear is in the range of that found in the liver (27.0 μg/gm ± 5.17 μg). These data are summarized in Figure 2.

Compounds with vitamin A activity are found in mammalian cells in the range of 1 μg/gm of tissue.[9] The main storage site of vitamin A is the parenchymal cell of the liver.[10] The vitamin A concentration of liver varies widely from one species to another, but is generally at least one order of magnitude higher than in other tissues. The concentration of vitamin A in the pooled tissue of the inner ear of the guinea pig was found to be ten times as high as in these other tissues.

Although the mere presence of an inordinate amount of an organic substance in a particular tissue does not prove that it plays a functional role, it is highly suggestive that such a relationship exists. The presence of high concentrations of vitamin A in the cochlea lends credence to the hypothesis that all special sensory receptor cells contain, or are functionally dependent upon, vitamin A.

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VOCAL CORD PARALYSIS AND THYROID SURGERY

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SUMMARY — A technique used to identify the recurrent and superior laryngeal nerves using a flexible fiberoptic bronchoscope is presented. The author has used this technique in 12 cases and found it superior to other techniques that he has tried.

Injury to the laryngeal motor nerves causes varying degrees of disability. Wagner[1] and Grossman[2] proposed the theory that total paralysis of the recurrent nerve immobilizes the vocal cord in the paramedian position, while paralysis of the recurrent and superior laryngeal nerves immobilizes the cord in the intermediate or open position. This open or cadaveric position was explained by Luschka[3] who described the elastic membrane as being dominant after death or in the denervated larynx.

The patient with one or both superior laryngeal nerves injured has no breathing difficulty but will complain of loss of quality in the higher registers of his voice. The patient with one recurrent nerve injured will have no breathing difficulty, but he will have a change in the quality of his voice. His voice will improve with time as fibrosis pulls the paralyzed cord to the midline. The patient may not recognize his injury unless told about it.

The person with bilateral superior and inferior laryngeal paralysis will breathe well since his cord will be pulled open by the elastic membrane. His voice will be very poor and breathy. As months pass, these cords will fibrose and eventually come to the midline, causing an improvement in the voice. A minor respiratory infection may cause the sudden death of the patient or he may simply experience chronic respiratory insufficiency for the remainder of his life. The patient with bilateral recurrent nerve injury but with intact superior laryngeal nerves is usually in acute trouble and often needs an immediate tracheostomy. His cords will both lie in the paramedian position and the least stimulation will cause complete closure of his larynx.

In the author's series of 52 thyroid surgeries, since 1973, 19% of these thyroids were malignant. In a series of 112 cases since 1968, 14% were malignant. The incidence of malignancy in thyroid tumors varies from author to author. It may be as high as 25% or lower than 10%. The high incidence of malignancy requires that a total hemithyroidectomy with exposure and preservation of the recurrent laryngeal nerve be done in most tumors involving one lobe. At least one parathyroid should be identified and preserved. The isthmus should be removed with the lobe containing the tumor. A frozen section is helpful in determining the approach to the opposite lobe. If the surgeon is certain about the integrity of the laryngeal nerve and one parathyroid gland, he may proceed with the opposite side if it is indicated by the permanent or frozen section. To attempt to go back and remove a remaining portion of an operated thyroid lobe is very dangerous to the recurrent nerve (Fig. 1).

The following case history demonstrates the value of a total hemithyroidectomy with identification and preservation of the recurrent nerve and one parathyroid gland.

A 22-year-old female complained of swelling in the area of the right lobe

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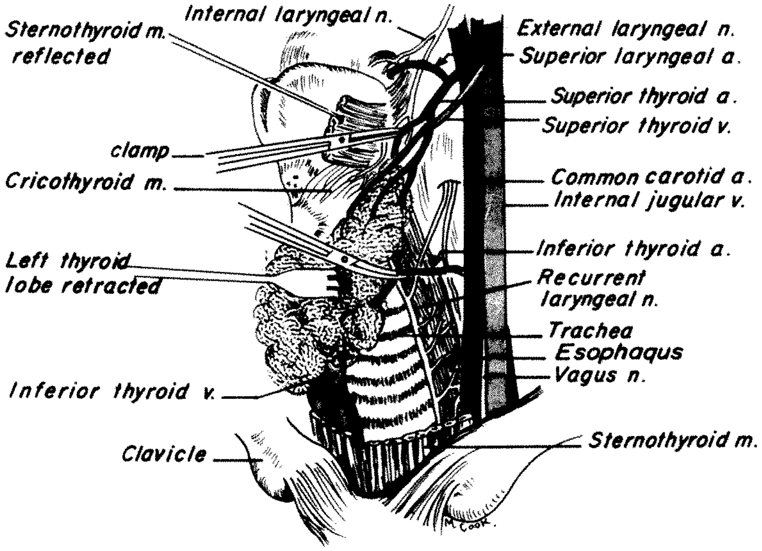

Fig. 1. Distribution of nerves and arteries to the thyroid gland with two areas of danger designated where the superior and inferior thyroid arteries cross the laryngeal nerves.

of the thyroid gland. A total right hemithyroidectomy with preservation of the recurrent nerve and one parathyroid gland was performed. A frozen section was done and reported as a follicular adenoma with atypism. The patient was discharged from the hospital on the second postoperative day. On the third postoperative day, the pathology department notified the surgeon that the frozen section was incorrect and the diagnosis was follicular carcinoma of the thyroid. On the seventh postoperative day the wound was opened and a total hemithyroidectomy was done on the left side. Three days after surgery the patient was discharged. She subsequently received cobalt and is now on thyroid medication. She has had a complete ablation of her thyroid. The original total hemithyroidectomy with preservation of the recurrent nerve and one parathyroid gland has improved the prognosis of the patient.

Lahey[4] advocated the identification and preservation of the recurrent laryngeal nerve in almost all thyroid surgery. Not all thyroid surgeons agreed with Lahey. Prioleau[5] wrote, "It is an axiom of thyroid surgery that a recurrent nerve seen is injured." Kent and Sawyer[6] oppose the routine exposure of the inferior laryngeal nerve on the grounds that if the procedure were carried out routinely by the average surgeon, there would be a greater number of surgically demolished recurrent laryngeal nerves than if the anatomy of the recurrent laryngeal nerve remained a complete enigma to the operator. Over a 23-year-period Riddell[7] reported on 1,700 thyroidectomies in which 2,507 nerves were risked. There was a 6% injury rate for the unidentified nerves and a 2% incidence for injury in 1,056 identified nerves. As a safeguard against bilateral abductor paralysis, Riddel advocated that at least one nerve be identified in all bilateral thyroidectomies. He recommended that the nerve be stimulated with an electric current and the integrity of the nerve be established by direct laryngoscopy during the operation before proceeding to resect the opposite lobe.

The advice of Riddell[7] was apparently taken by surgeons. Techniques have been developed to determine the integrity of the recurrent nerves. All of the techniques thus described have definite limitations. The technique as described by Riddell requires that the anesthetist expose the cords during surgery while the surgeon stimulates the recurrent nerve. This is always a difficult feat and sometimes an impossible one due to the surgical drapes or the configuration of the patient's teeth, jaw, or larynx.

Shedd and Burget[8] used an intralaryngeal balloon to record pressure changes in the larynx as the recurrent laryngeal nerve was stimulated. This requires considerable specialized equipment and the accurate placement of the balloon in the larynx.

An electromyographic technique was described by Flisberg and Lindholm.[9] Needle electrodes were inserted through the cricothyroid membrane so that the tips of the needles were in the vocal cord. This seems a difficult technique requiring special equipment.

Kratz[10] described a technique using an operating microscope and 3V facial nerve stimulator. In this technique the larynx can be seen to move by external observations as the recurrent nerve is stimulated. This technique required that the larynx be mobile. The isthmus must first be cut. The disadvantage of the technique is that large tumors obstruct the view of the larynx and impede its motion.

FLEXIBLE FIBEROPTIC BRONCHOSCOPE TECHNIQUE FOR IDENTIFICATION OF THE RECURRENT NERVE

The patient is anesthetized with a small 26 endotracheal tube. A plaget of cotton saturated with a vasoconstrictor is placed in the nose. When the time comes to identify the nerve, the cotton is removed and a flexible bronchoscope is passed through the nose. The end of the scope is placed one and one half inches above the cords. A common error is to get the end of the scope too close to the cords. The recurrent nerve is then stimulated while the cords are observed. Motion is also caused by stimulation of the superior laryngeal nerve.

This is a simple test requiring the usual skills possessed by the anesthetist. A flexible bronchoscope and a 3V facial nerve stimulator are available in most modern operating rooms.

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CRICOTHYROID MUSCLE IN RESPIRATION

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SUMMARY — Although the phonatory activity of cricothyroid muscle is well-known, its respiratory role often remains unrecognized. Recent data suggest this muscle plays a major role in the overall regulation of breathing by its control of expiratory resistance and flow. Cricothyroid contraction in expiration results in vocal elongation increasing glottic size. Such a mechanical effect reduces airway resistance and shortens expiratory duration. By such a mechanism, the rate of respiration may ultimately be modified using the larynx as the principal effector of this control. In this regard, cricothyroid expiratory activity is a pressure-sensitive evoked response influenced by afferent vagal stimuli. Its activity is triggered by a critical threshold of pressure-increase with respect to time, and its duration is directly dependent on the duration of positive subglottic pressure. The threshold of cricothyroid activation is reduced in hypercapnia and elevated in hypocapnic states.

Neurally controlled retardation of expiratory airflow is an essential characteristic of normal breathing. In eupneic states expiratory flow and duration are principal determinants of respiratory frequency. As others have demonstrated in both animal and human investigations, variations in respiratory rate result primarily by changing the duration of the expiratory phase rather than the inspiratory phase of the respiratory cycle.[1,2] In this regard the larynx exerts a major valvular effect on ventilatory resistance significantly influencing both the inspiratory and expiratory phases of respiration. On the one hand, inspiratory resistance is primarily controlled by phasic abduction produced by the posterior cricoarytenoid muscle.[3,4] On the other hand, the mechanism of expiratory resistance has remained unclear in terms of passive laryngeal elasticity or active muscular participation. The basis of this confusion stems in part from an unfortunate misinterpretation of earlier laboratory data.

Since others have been unable to document phasic expiratory contraction in thyroarytenoid or lateral cricoarytenoid muscles during eupneic breathing,[5,6] we have therefore focused our attention on the respiratory characteristics and feedback control of the cricothyroid muscle. This investigation concerns the elucidation of cricothyroid activity in its possible role as a regulator of laryngeal resistance through the mechanism of phasic vocal elongation during expiration. Such an understanding contributes to the growing recognition of the larynx as a significant effector of expiratory resistance and therefore respiratory control.[7,8]

METHODS AND MATERIALS

Twenty-one adult dogs were used in this study. Pentobarbital sodium, 25-30 mg/kg, was administered intraperitoneally. Constant anesthesia levels were maintained in Stage III, Plane I by periodic augmentation of pentobarbital administered through a venous cannula. The animal was then placed supine on the operating table and the larynx and trachea were exposed through a vertical midline incision. A tightly fitting tracheostomy tube was inserted at the level of the fifth tracheal ring and intratracheal pressure change was measured through a transtracheal needle connected to a Statham p-23 BC pressure transducer.

The sternohyoid and sternothyroid muscles were resected to expose the framework of the larynx and trachea. The recurrent laryngeal nerves were sectioned bilaterally in order to

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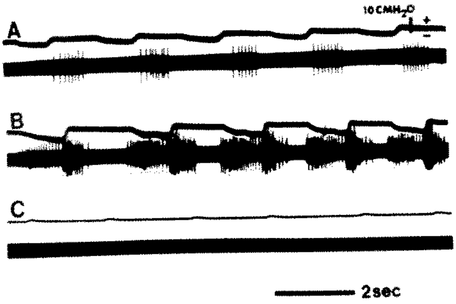

Fig. 1. Cricothyroid response to ventilatory loading in the spontaneously breathing animal. (A) Untracheostomized, eupneic breathing. Upper tracing represents tracheal pressure. Lower tracing represents cricothyroid electromyography. (B) Upper airway obstruction. (C) Tracheostomized breathing. Note that mild ventilatory loading elicits expiratory activity whereas moderate loading produces inspiratory and expiratory cricothyroid activity.

minimize electrical contamination produced by the contraction of adjacent intrinsic musculature. Electromyographic activity was recorded with modified Hirano-hooked wire electrodes inserted into the cricothyroid muscle.

Constant body temperature, monitored with a rectal thermometer, was maintained with a heating pad placed beneath the anesthetized animal. Blood pressure measurements were obtained through a femoral artery cannula and blood gas analysis performed with a Radiometer acid-base analyzer PHM-72. Electromyographic data were displayed oscilloscopically and photographed with a Grass kymograph camera.

RESULTS

Over 200 electromyographic patterns of cricothyroid activity, obtained from 21 dogs, are summarized with respect to varying respiratory states.

During untracheostomized eupneic breathing, cricothyroid activity is primarily observed in expiration (Fig. 1, Line A).

As mechanical resistance to ventilation is increased, both inspiratory and expiratory activity correspondingly increase (Fig. 1, Line B), whereas the removal of resistance results in cessation of all electromyographic activity (Fig. 1, Line C). The dyspneic inspiratory activity of cricothyroid muscle, which has been thoroughly described by Suzuki et al,[9] involves cricothyroid contraction in both the inspiratory and expiratory phases of respiration.

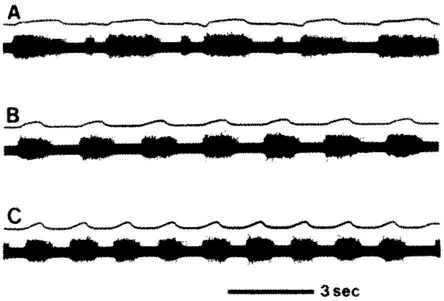

Fig. 2. Cricothyroid response to mechanical ventilation at rates of (A) 20 per minute, (B) 30 per minute, (C) 40 per minute. Note the synchronous tracking of cricothyroid to positive pressure stimuli.

A closer look at expiratory activity of cricothyroid muscle may provide further insight into its laryngeal influence on respiration. What factors govern cricothyroid activity? And what is its possible role in ventilatory control?

If one places an animal on a mechanical respirator the following interesting phenomenon is observed. Cricothyroid activity is evoked by positive intratracheal pressure, its contraction synchronized with the movements of the respirator (Fig. 2, Line A). When the respiratory rate is mechanically increased from 20 to 40 per minute, cricothyroid activity appears to track synchronously with this rate change (Fig. 2, Lines B, C).

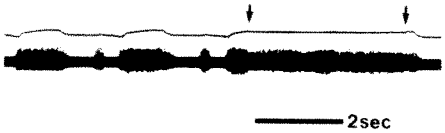

Fig. 3. Duration of positive pressure stimulation determines duration of cricothyroid evoked activity.

When the respirator is stopped in midexpiration, cricothyroid activity continues as long as positive intratracheal pressure is maintained (Fig. 3). When pressure decreases, cricothyroid activity ceases. These results suggest that positive intratracheal pressure is an important determinant of cricothyroid ex-

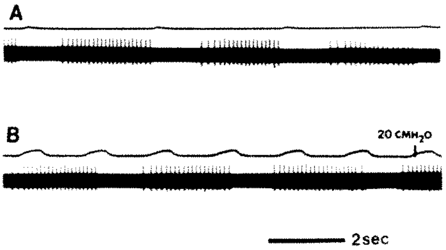

Fig. 4. (A) Vagotomy produces spontaneous inspiratory hyperactivity of cricothyroid motoneurons. (B) Following vagotomy, positive pressure ventilation no longer triggers cricothyroid activity. Cricothyroid tracking is therefore abolished.

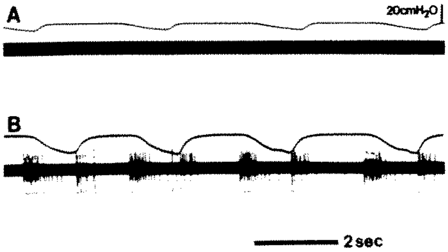

Fig. 5. (A) In the tracheostomized normocapnic animal, cricothyroid muscle is silent. Upper tracing represents esophageal pressure. Lower tracing represents cricothyroid electromyography. (B) In the tracheostomized hypercapnic animal, cricothyroid contracts in both inspiration and expiration.

piratory participation and that expiratory cricothyroid contraction, unlike its inspiratory activity, is essentially a peripherally evoked response which does not originate spontaneously at the medulla.

After bilateral vagotomy, cricothyroid tracking is therefore totally abolished, suggesting the importance of vagal afferents in the mediation of this evoked reflex. Rather, vagotomy produces cricothyroid inspiratory predominance by the following mechanism (Fig. 4, Line A). Because the vagus is largely inhibitory to the respiratory center, vagotomy releases inspiratory neurones into spontaneous phasic hyperactivity. However, note that positive pressure stimuli no longer evoke a cricothyroid response following vagotomy (Fig. 4, Line B). These data therefore strongly suggest that vagally mediated afferent influences play a direct role in the elicitation of cricothyroid contraction during the expiratory phase of respiration.

On the other hand, there is little question that the primary and dominant stimulus to respiratory control is chemical, consisting of direct CO$_2$ effect on respiratory motoneurons, including those motoneurons of the cricothyroid muscle. The following series of data confirm this observation and demonstrate the secondary role of vagal afferents on those motoneurons of the cricothyroid.

In the tracheostomized normocapnic animal, cricothyroid muscle is silent (Fig. 5, Line A). We would expect this result since cricothyroid motoneurons are neither stimulated by CO$_2$ excess nor by peripheral vagal influences. After 10% CO$_2$ administration, cricothyroid is activated both in inspiration and expiration in much the same way that would be produced in the normocapnic animal exposed to ventilatory loading (Fig. 5, Line B).

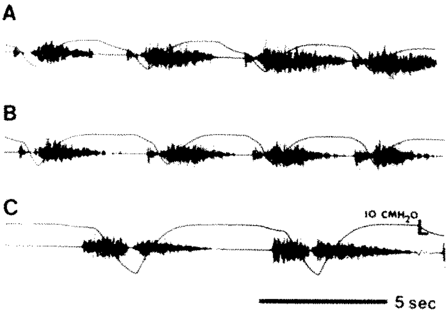

Fig. 6. In the tracheostomized hypercapnic animal, stepwise vagotomy produces cricothyroid inspiratory predominance as its expiratory activity diminishes. (A) Cricothyroid electromyography and esophageal pressure curve prior to vagotomy. (B) Cricothyroid electromyography and esophageal pressure after unilateral vagotomy. (C) Cricothyroid electromyography and esophageal pressure after bilateral vagotomy.

However, in the tracheostomized animal subjected to hypercapnia, cricothyroid activity in expiration clearly diminishes as bilateral vagotomy is stepwise completed (Fig. 6). When crico-

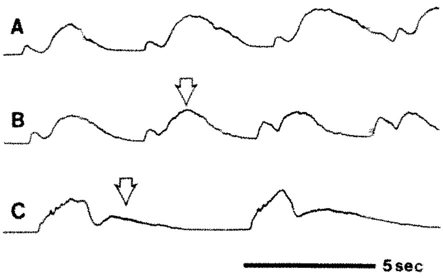

Fig. 7. Integrated electromyography of cricothyroid activity in the hypercapnic state. (A) prior to vagotomy, (B) after unilateral vagotomy, (C) after bilateral vagotomy. Note progressive inspiratory cricothyroid predominance and expiratory diminution produced by vagotomy.

thyroid discharge is electronically integrated, this effect becomes even more apparent, confirming the primary chemical influence on expiratory motoneuron activity and the secondary peripheral vagal influence on cricothyroid respiratory control (Fig. 7).

From this we conclude that, unlike normocapnic circumstances, hypercapnia produces *spontaneous* activity of cricothyroid motoneurones both in inspiration and expiration but that peripheral, vagally mediated afferent influences determine their final level of participation.

Of further interest, in the unvagotomized preparation, duration of cricothyroid expiratory activity is influenced by continued positive intratracheal pressure. It would therefore also be appropriate to identify the triggering mechanism for cricothyroid activity and its modification by the chemical drive.

Current observation suggests that under normocapnic conditions the rate of intratracheal pressure change appears critical to cricothyroid elicitation. That is to say, a rapid rise in tracheal pressure is more likely to initiate cricothyroid activity than a gradual rise in pressure regardless of the absolute pressure amplitude obtained. Threshold of this cricothyroid evoked response in normocapnia can then be ascertained with respect to a critical dP/dt. This critical level of pressure change with respect to time measures approximately 30 cm H_2O/sec (Fig. 8).

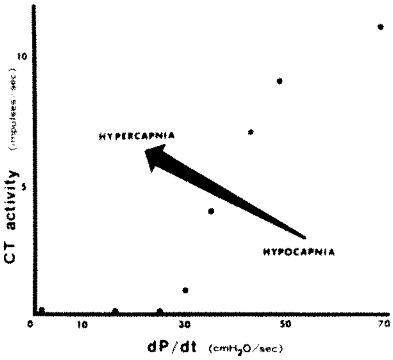

Fig. 8. The threshold of cricothyroid elicitation in response to rate of tracheal pressure change measures 30 cm H_2O/sec in normocapnia. Hypercapnia reduces cricothyroid threshold whereas hypocapnia raises its threshold.

Hypercapnia, on the other hand, shifts this threshold to the left. That is to say, lower rates of pressure-rise are required to trigger cricothyroid activity during hypercapnia. Conversely, these data suggest that this threshold is elevated in hypocapnic states by a threshold shift to the right (Figs. 8 and 9).

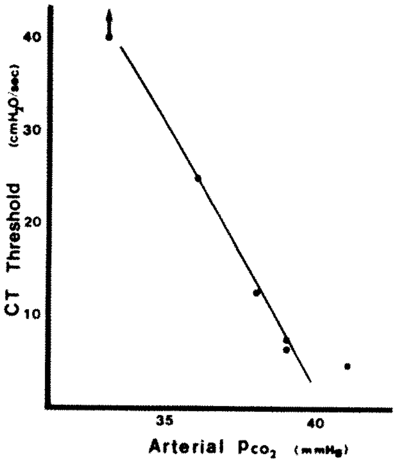

Fig. 9. The quantitative relationship of cricothyroid threshold (expressed in cm H_2O/sec) is defined with respect to arterial CO_2. Hypocapnia raises the threshold while hypercapnia reduces it.

DISCUSSION

The relevance of these data lies in a

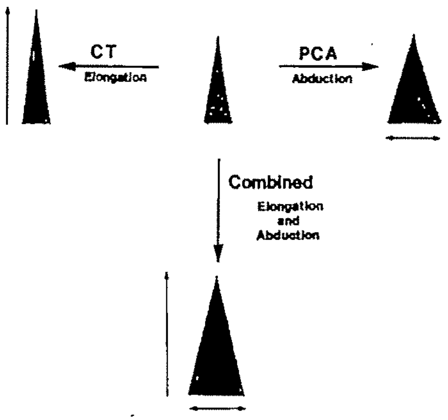

Fig. 10. Glottic alteration produced by cricothyroid and posterior cricoarytenoid action alone and in combination. Combined muscle action maximizes the cross-sectional area of the laryngeal aperture.

brief review of cricothyroid action on the valvular configuration of the glottic aperture. According to Arnold[10] the action of unopposed cricothyroid contraction results in vocal: 1) adduction, 2) tensing, and 3) elongation.

The first two, adduction and tensing, play a major role in phonatory laryngeal function. On the other hand, we believe that vocal cord elongation, produced by cricothyroid contraction, is primarily a respiratory activity. Hast[11] reports cricothyroid contraction lengthens the relaxed cord by 30%. Such action expands the glottic aperture in its anteroposterior direction, while its horizontal dimension is regulated by the pivotal movement of the cords produced by posterior cricoarytenoid contraction. The combined action of the cricothyroid and posterior cricoarytenoid therefore results in maximum glottic size as demonstrated in Figure 10.

The valvular mechanism of laryngeal constriction during expiration is therefore based on the following understanding. During expiration, the cross-sectional area of the laryngeal aperture is reduced by virtue of elastic recoil, assuming a cadaveric configuration in midexpiration. However, the rate of recoil, we believe, is regulated by active muscular participation.

On the one hand, Remmers and Bartlett[3] have indicated that expiratory laryngeal resistance is regulated by continued posterior cricoarytenoid activity well into the expiratory phase of respiration. Such abductor activity in early expiration retards elastic collapse of the glottis, acting in turn to retard the braking mechanism of the larynx. Cricothyroid action in conjunction with this posterior cricoarytenoid activity therefore not only maximizes the effective cross-sectional area of the laryngeal aperture but provides a greater degree of regulatory potential with respect to the fine control of expiratory resistance. Based upon the neural regulation of cricothyroid muscle, its expiratory activity therefore appears to play a significant role in the direct control of expiratory laryngeal resistance and indirectly in the overall control of respiration itself.

Current data suggest the following conclusions:

1. Laryngeal resistance contributing to expiratory braking is fundamentally produced by elastic recoil of the larynx.

2. The rate of recoil producing passive glottic constriction is modified by cricothyroid and posterior cricoarytenoid contraction during expiration.

3. In normocapnia, expiratory cricothyroid activity is clearly an evoked pressure-sensitive response.

4. Expiratory cricothyroid activity is triggered by a critical rate of elevation in subglottic pressure transmitted to pulmonary vagal receptors, the effect of which may be abolished by vagotomy.

5. This critical threshold of dP/dt measures 30 cm H_2O/sec in normocapnia. In hypercapnia lesser dP/dt appears necessary for this elicitation, while hypocapnia raises the threshold of expiratory cricothyroid activity.

6. The duration of cricothyroid expiratory contraction is principally governed by the presence of positive subglottic pressure and is inhibited by a negative dP/dt.

7. The cross-sectional area of the glottis, we feel, modified by expansion of the laryngeal aperture in its antero-

posterior dimension, is a direct effect of cricothyroid activity. That is to say, the greater the rise in subglottic pressure, the larger the laryngeal aperture in expiration. The sensitivity of this reflex action appears to be governed by the level of arterial CO_2 tension.

8. It follows that the larger the expiratory laryngeal lumen, the shorter the expiratory duration resulting in an increased rate of breathing in response to rising CO_2 arterial tension.

9. Because the regulation of expiratory duration is a major determinant of respiratory frequency, we feel the cricothyroid muscle in conjunction with posterior cricoarytenoid participation, represent principal laryngeal effectors of this control.

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XII WORLD CONGRESS OF OTORHINOLARYNGOLOGY

The XII World Congress of Otorhinolaryngology will be held June 21-26, 1981 in Budapest, Hungary. Preliminary communications, recommendations and suggestions, should be directed to Prof. Dr. L. Surján, President, XII World Congress of ORL, H-1389 Budapest, Pf: 112 Hungary.

Ann Otol 87:1978

ALCOHOL AND THE OCULOMOTOR SYSTEM

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SUMMARY — The influence of alcohol on the oculomotor system was observed by means of the caloric eye tracking pattern (CETP) test, the visual suppression test on caloric nystagmus, and the positional nystagmus, eye tracking and gaze nystagmus tests. In Group A (nine cases whose CETP before the intake of alcohol was normal), the influence of alcohol consumption appeared regularly and consistently in the following order: abnormality of CETP ≥ positional alcohol nystagmus ≥ abnormality of the eye tracking pattern ≥ alcohol gaze nystagmus. On the contrary, in Group B (eight cases whose CETP before the consumption of alcohol was already abnormal), with one exception, the regularity noted in Group A was not observed. This phenomenon may be attributable to the presence of latent disorders of the oculomotor system. In both groups, the duration of the caloric nystagmus itself was slightly shortened and its amplitude somewhat suppressed after the consumption of alcohol. The results were confirmed by experiments in which the subjects kept their eyes open in darkness. On the other hand, when the eyes were kept open in light surroundings, the duration and amplitude of the caloric nystagmus were exaggerated in appearance because the mechanism of visual suppression was disturbed by alcohol.

It is well-known that acute alcohol poisoning affects the oculomotor system and results in positional and gaze nystagmus.[1,2] Furthermore, the influence of alcohol on smooth pursuit eye movement has been the object of research in recent years.[3] From our present study, we noted that the influence of alcohol on the caloric eye tracking pattern (CETP)[4] was seen earlier than with any other neurotological test. This report seeks to clarify if there is any law of appearance among Type 1 positional alcohol nystagmus (PAN), alcohol gaze nystagmus (AGN), abnormalities of the eye tracking pattern and abnormalities of the CETP when the oculomotor system is affected by alcohol. We investigated 17 cases of acute alcohol toxicity by means of the positional nystagmus, gaze nystagmus, eye tracking and the CETP tests.

MATERIALS AND METHODS

MATERIALS

Seventeen healthy female volunteers, nurses, aged 20 to 24, were tested. In the otological (hearing and caloric) and standard neurological examinations administered to all of them, no abnormalities were noted. Furthermore, the results of gaze nystagmus and eye tracking tests were also normal. However, the volunteers were divided into two groups on the basis of the results of the CETP test: Group A (nine cases) in which no abnormalities were seen and Group B (eight cases) in which irregularities were observed, indicating some disorders in the oculomotor system.

METHODS

1. The positional nystagmus test was administered to the subjects with their eyes open in a dark room.
2. The gaze nystagmus test was performed during 30° eye deviations to the right and to the left in the same room, lighted.
3. The eye tracking test consisted of pursuing a target which moved in a pendular fashion 70 cm in front of the subject at 0.3 cycle/sec. The target subtended a visual arc of 40° and pursuit eye movements were recorded as the eye tracking pattern (ETP). The three above tests were repeated every five to seven minutes in principle.
4. For the CETP test, the left ear was irrigated with 20 cc of ice water for 10 seconds. We administered the eye tracking test for 20 seconds beginning 50 seconds after the start of the ice water injection.[4] The pattern thus measured is called the caloric eye tracking pattern. The duration of the caloric nystagmus was also measured in light (Table 1).
5. In addition, we also performed the visual suppression (VS) test on seven cases selected at random. Caloric stimulus was applied in

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TABLE 1. ALCOHOL AND THE DURATION OF CALORIC NYSTAGMUS (IN SEC)

	In Darkness			*In Light*		
		With Alcohol			*With Alcohol*	
Exp.	*Without Alcohol*	*1st Exam.*	*2nd Exam.*	*Without Alcohol*	*1st Exam.*	*2nd Exam.*
1				100	120	170
2				90	90	100
3	210	190		140	160	
4	270	240	260	100	130	
5	210			120	120	160
7				120	150	
9				120	180	
10	200	200	190	120	130	
11	220	210				
12				120	140	145
13	240	220		90	160	
14				130	140	180
15	180	150	160	107		
16				120	140	130
17				120	130	130

light by the same method as in the CETP test. The subject was then put in darkness. The light was turned on for 10 seconds beginning 50 seconds after the start of the ice water irrigation, then turned off again until the caloric nystagmus disappeared. The duration of the caloric nystagmus was also measured in darkness (Table 1). Visual suppression was defined as the percentage reduction in slow phase velocity of the eyes due to visual fixation (i.e., percentage of VS = 100 x (slow phase velocity in the dark — slow phase velocity in light) ÷ slow phase velocity in the dark).[5]

6. The CETP test and the VS test were not administered to each subject more than three times a day because caloric irrigation after the consumption of alcohol was disagreeable.

7. In order to avoid the influence of caloric irrigation, we did not perform the positional nystagmus, gaze nystagmus or eye tracking tests until at least seven minutes after the start of ice water irrigation for the CETP or VS tests.

8. All of the above tests were administered to the subjects beforehand with no prior alcohol consumption and then on another day subsequent to the intake of alcohol.

9. Scotch whiskey in the amount of 100 ml was consumed orally over a period of two to three minutes. In some cases, an additional 50 ml were given.

10. In all cases, the testing was completed within two hours.

11. All eye movements were recorded with the aid of the ENG.

RESULTS

GROUP A

Experiment 1 (Subject, age 21). The CETP test, performed 12 minutes after the start of consumption of 100 ml of alcohol, produced a slight but constant abnormality. At this time, neither PAN nor AGN were observed and the ETP was also normal. Positional alcohol nystagmus appeared at 22 minutes and 50 ml of alcohol were added at 25 minutes. The appearance of abnormalities of the ETP was noted at 45 minutes. Then, at 70 minutes, 50 ml of alcohol were added again. Alcohol gaze nystagmus appeared at 76 minutes and, at 94 minutes, the CETP test disclosed severe abnormalities. These findings, as recorded by the ENG, are shown in Figure 1 and diagrammed in Figure 2, Experiment 1.

Experiment 2 (Subject, age 21). Slight abnormalities in the CETP were found at seven minutes. Then PAN, abnormalities of the ETP and AGN appeared one after another. At 30 minutes, the CETP became markedly abnormal, whereas only slight irregularities were noted in the ETP (Figs. 2 & 3).

Experiment 4 (Subject, age 24). Posi-

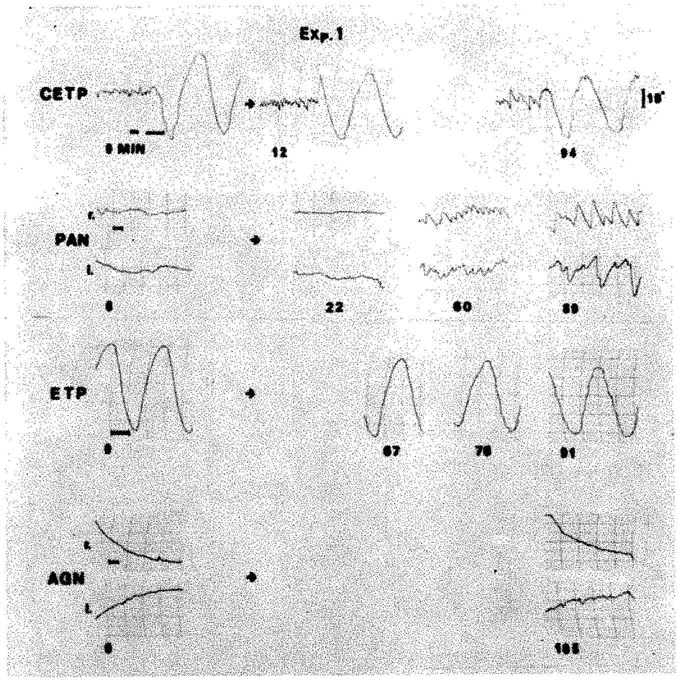

Fig. 1. Influence of alcohol on the oculomotor system (ENG record from Experiment 1). Numerals indicate the time in minutes from the beginning of consumption of alcohol (0 min - Before consumption of alcohol). Each horizontal bar corresponds to one second. Calibration of 10° is indicated by a vertical bar on the right side. CETP - Caloric eye tracking pattern; PAN - Positional alcohol nystagmus (r - Lateral right position; l - Lateral left position); AGN - Alcohol gaze nystagmus (r - Right lateral gaze; l - Left lateral gaze); ETP - Eye tracking pattern.

tional alcohol nystagmus and ETP abnormalities both appeared at 12 minutes, but AGN was not observed until 110 minutes (Fig. 2).

The results of our findings on Group A are summarized as follows:

1. The influence of alcohol on the oculomotor system was disclosed by the CETP test earlier than by the conventional eye tracking test.

2. Abnormalities of CETP and PAN appeared at almost the same time.

3. Though they often appeared simultaneously, PAN frequently was observed a little earlier than ETP abnormalities.

4. Alcohol gaze nystagmus appeared last.

GROUP B

In this group, whose CETP was already abnormal before the consumption of alcohol, it was often difficult to determine the effect of its consumption on the CETP, nor could we find any law of appearance among PAN and the abnormalities of the ETP and AGN.

Experiment 12 (Subject, age 21). Eye tracking pattern abnormalities appeared earlier than PAN and AGN (Fig. 2).

Experiment 13 (Subject, age 21). Alcohol gaze nystagmus appeared earlier than ETP abnormalities and PAN (Fig. 2).

Experiment 16 (Subject, age 23). Alcohol gaze nystagmus was not observed (Fig. 2).

VISUAL SUPPRESSION TEST

Vestibular nystagmus is suppressed by visual fixation. This phenomenon is called visual suppression (VS). The VS mechanism is not well understood, but it is known that the flocculonodular lobe (FNL) plays an important role in maintaining its function. This is sup-

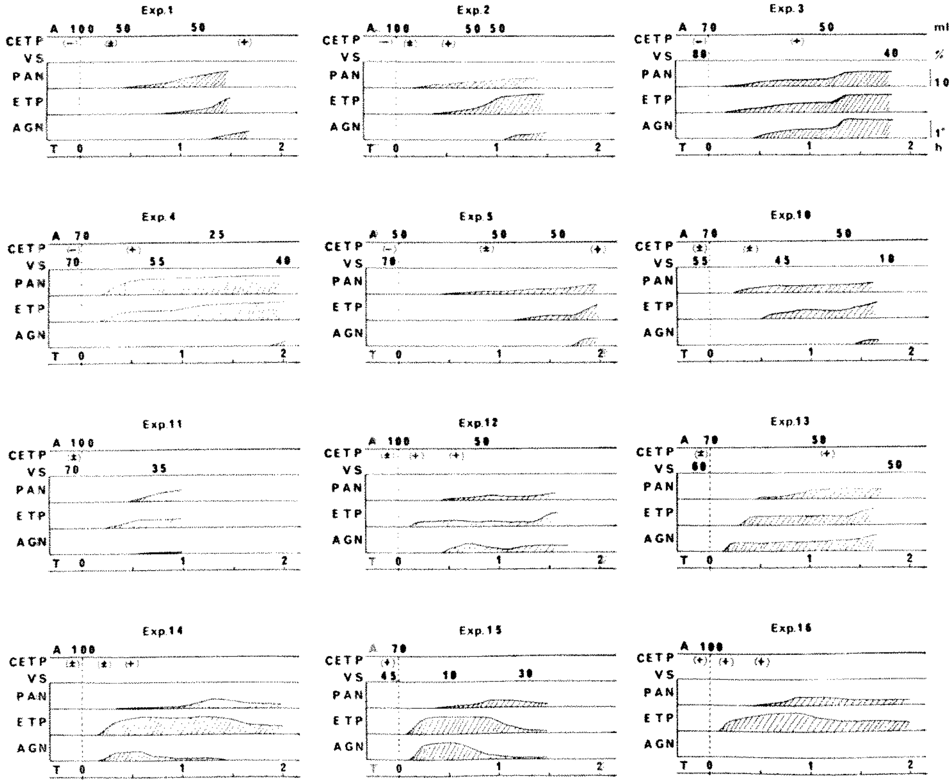

Fig. 2. Results of the alcohol test. A - Alcohol (Numeral indicates milliliters consumed at each time point); T - Time (from beginning of consumption in hours). For CETP, (−) - normal, (±) - slightly abnormal; (+) - evidently abnormal. For visual suppression (VS), numerals indicate percentage of VS. The calibrations are shown by the vertical bars at the right end: 10° for PAN, 1° for AGN. A 10° calibration of PAN means that the average amplitude (total amplitude/number of nystagmus beats during 20 seconds) is 10° or more. Also AGN is calibrated in such a way that a more than 1° average amplitude would be assigned 1°. It is difficult to show ETP quantitatively, so that an abnormality presenting the same degree as that at 91 minutes in ETP as in Figure 1 is considered to be maximum, and any abnormality more severe in degree is also assigned the maximum value.

ported by the results of animal experiments in which it was found that caloric nystagmus is exaggerated by stimulation of the FNL[6] and that VS on caloric nystagmus is disturbed by lesions of the FNL.[7]

In our study, the VS test was performed on seven cases. From the results shown in Figure 2, it was ascertained that the VS mechanism is disturbed by alcohol consumption. Figure 4 shows the ENG records of the VS tests in Experiments 3 and 10, from which the following three points are summarized:

1. With the eyes opened in a dark room, the amplitude and eye speed of caloric nystagmus (at 117 minutes for Experiment 3 and 104 minutes for Experiment 10) were suppressed in comparison with those at 0 minute.

2. But with the eyes opened in the same room when lighted, the amplitude of caloric nystagmus after alcohol intake was exaggerated.

3. The VS function at 0 minute (80% in the case of Experiment 3 and 55% for Experiment 10) fell off to 40% at 117 minutes and 10% at 104 minutes, respectively.

These findings allow us to say that alcohol slightly suppresses caloric nys-

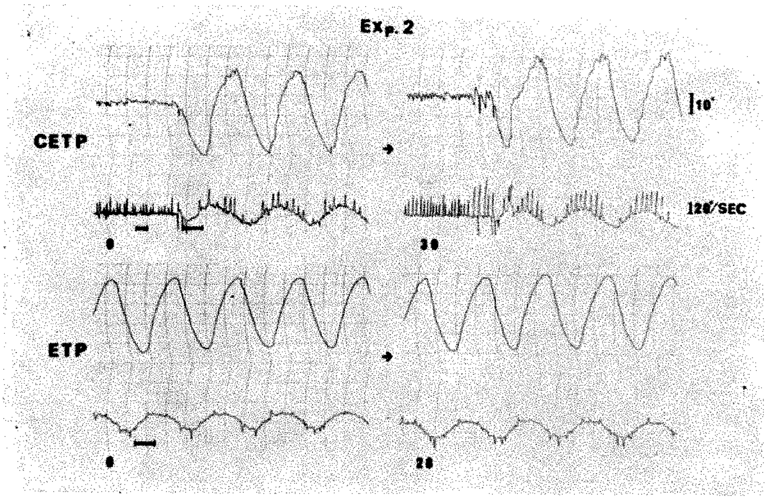

Fig. 3. (Exp. 2) Alcohol affects the CETP earlier than the ETP. Each upper trace of the CETP and ETP indicates the ENG of the eye movement (time constant 3.0 sec) and the lower traces are differentiated ENG of the upper traces (time constant 0.03 sec). Each horizontal bar indicates one second, and the calibrations are shown by the vertical bars on the right side. Numerals indicate the time from the beginning of consumption of alcohol in minutes.

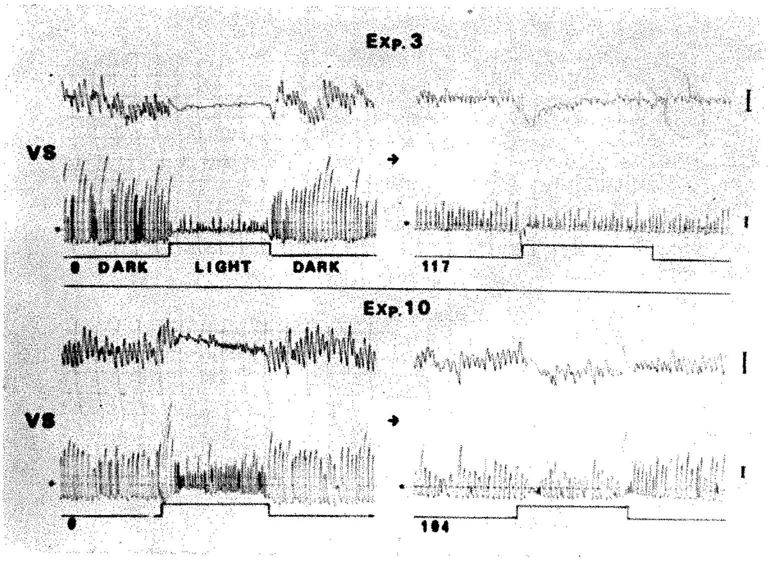

Fig. 4. (Exps. 3 and 10) Caloric nystagmus is suppressed in light. Before consumption of alcohol, the function of VS was within normal limits, but it was reduced with the consumption of alcohol. * - Base line of the ENG record. Time scale and calibrations are the same as those of Figure 3. Dark - Eyes open in darkness; Light - Eyes open in light.

tagmus itself in the dark, but in the light the amplitude of caloric nystagmus is exaggerated in appearance because the VS function is weakened by alcohol.

The duration of the caloric nystagmus was measured in darkness (VS test) and in light (CETP test) and the results are shown in Table 1, indicating that in darkness the duration was a little shortened after the consumption of alcohol but that in light, on the contrary, it was lengthened in appearance. This may be attributed to a VS disorder.

DISCUSSION

Alcohol and the CETP Test. It may be said that the CETP test enables us to observe if there is any disorder in the oculomotor system or not. In all cases, CETP abnormalities were observed subsequent to alcohol intake and appeared before those produced by any other test.

Positional Alcohol Nystagmus. The mechanism of PAN is not clearly understood, but the following points were noted:

1. Alcohol affects the cerebellum first.
2. Visual suppression function is affected by alcohol.
3. Positional alcohol nystagmus appears at a relatively early stage after the consumption of alcohol.
4. Visual suppression function is disturbed by FNL lesions.[7]
5. Flocculonodular lobe lesions produce positional nystagmus.[6,8]

Eye Tracking Test. Smooth pursuit eye movement is controlled mainly by the cerebellar cortex and also by the brain stem. However, it is difficult to determine the lesion accurately just on the basis of the type of abnormality present. But the slight abnormality of the ETP observed at an early stage after alcohol consumption, manifested a slightly ataxic pattern originating from cerebellar disorders. Here, we note Wilkinson's[3] findings to the effect that alcohol influences the cerebellum earlier than the brain stem.

Alcohol Gaze Nystagmus. In our Group A, AGN appeared later than the abnormalities in the CETP, PAN and the irregularities of the ETP. And, in our observation, it continued for more than 20 seconds, which indicates that, even if it involves dysmetria of cerebellar origin, its durability shows that it is a gaze nystagmus due to brain stem disorders. Here, we must note that the ETP abnormalities appeared earlier than AGN. Thus, it follows that alcohol affects the cerebellum first and then the brain stem.

Law of Appearance of Abnormalities (CETP, PAN, ETP, AGN). In Group A, there was a law of appearance among the abnormalities of CETP, PAN and the abnormalities of ETP and AGN. We believe that, in normal subjects, alcohol affects the oculomotor system according to this law.

On the contrary, no such law was observed among the eight cases in Group B. This factor may be attributed to the presence of latent disorders in the oculomotor system. For example, in Experiment 13, AGN appeared before the ETP abnormalities. It is assumed that this may be caused by the presence of latent brain stem disorders which make it more sensitive to alcohol than the cerebellum.

CONCLUSIONS

In Group A, the influence of alcohol appeared regularly and consistently in the following order: CETP abnormalities $\geq$ PAN $\geq$ETP abnormalities $\geq$ AGN. In Group B, with the exception of one case, no such regularity was observed. We believe this is attributable to latent disorders in the oculomotor system.

The duration of caloric nystagmus itself was a little shortened by alcohol. This finding was confirmed by an experiment administered to subjects in darkness with their eyes open. On the other hand, when the eyes were kept open in light, the duration of caloric nystagmus was lengthened in appearance because the VS mechanism was disturbed by alcohol.

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THE DEAFNESS RESEARCH FOUNDATION

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TEMPORAL BONE FINDINGS IN HEMIFACIAL MICROSOMIA

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SUMMARY — The temporal bone findings in a case of hemifacial microsomia are described with photographs. The right facial hypoplasia was associated with anophthalmia and microtia on the same side. The right petrous bone was hypoplastic and showed total superior dehiscence of the internal acoustic meatus. The otic capsule was deformed with an underdeveloped cochlear modiolus grossly deficient in spiral ganglion population. The spiralling cochlear shell showed partial deficiency of the interscalar septum between the middle and apical coils. The cochlear duct was shorter than that on the normal side; the organ of Corti however was normal. The vestibular system did not show any structural abnormality except for the degeneration and reduction of the Scarpa's ganglion cells and nerve fibers. An additional interesting fact was that the facial nerve was totally absent in the temporal bone except for its nervus intermedius component.

Hemifacial microsomia is the name given to the unilateral hypoplastic deformity of the craniofacial area and is characterized by varying degrees of underdevelopment of the eye, the ear, the mandible, and the contiguous bony and soft tissue structures of the cranium and face. Variants of this entity have been specifically designated into several named syndromes (e.g., Goldenhar-Gorlin syndrome). The purpose of this article is to report the histopathological findings of the temporal bones in a case of hemifacial microsomia and to add a short nosological discussion on this entity.

CASE REPORT

This 2½ year-old child was born to a 36-year-old primigravida at full term. The baby was delivered with mid-forceps and the Apgar score was eight. Pregnancy had been uneventful except for vomiting in early pregnancy for which the mother took some unidentified antiemetic. There was no family history of congenital anomalies. Chromosome analysis of the infant carried out at Bellevue Hospital showed normal pattern.

The baby was born with multiple congenital anomalies (Fig. 1A, & B) including bilateral cleft lip, cleft palate and cleft nose. The right auricle was absent except for small lobular and tragal elements placed far forward on the cheek and attached loosely to the skin over the mandible. External auditory canal was absent. The right orbit was atrophic and empty. The maxilla and mandible were hypoplastic on the right side. The baby had no deglutition reflex and a gastrostomy had to be performed at the age of two months for feeding purposes. At the age of 2½ years the child was taken to the operating room for corrective surgery of the cleft palate. During the postoperative period the child developed massive aspiration pneumonia and died two days after surgery. At autopsy done 12 hours later both temporal bones were removed for examination.

Other anomalies noted at surgery: Multiple cervical hemivertebrae, congenital heart disease described as ventricular septal defect with a left to right shunt and mitral stenosis and Arnold-Chiari malformation in the brain.

Gross Appearance of the Right Petrous Bone. The right petrous bone was

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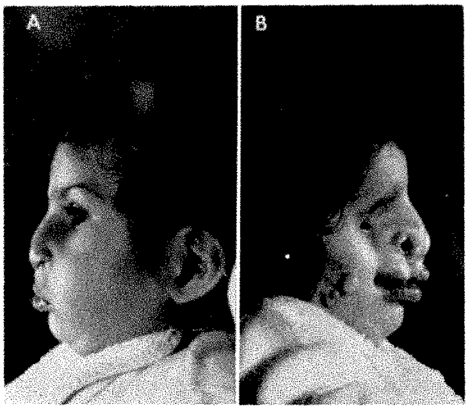

Fig. 1. Two views of the face. A) Nearly normal appearance of the left side of the face, except for low set ear. B) Characteristics of hemifacial microsomia: anophthalmia, nasal and lip deformities, sunken malar area, oral angle cleft and auricular remnants placed forward on the cheek skin.

smaller than the left one and appeared deformed. The petrous apex was flattened. The superior petrosal ridge could not be discerned. A deep furrow could be noticed on the anterosuperior surface of the petrous bone running forward and laterally from the posterior surface. This represented the position of the internal acoustic meatus that lay as a narrow groove in the floor of the furrow. Lateral to the furrow, the arcuate eminence presented a marked bulge.

Postmortem tomography of the petrous bones clearly showed the stenosed right internal acoustic meatus (Fig. 2).

External and Middle Ear. As mentioned before, the right auricle was represented by remnants of tragal and lobular tissue. The external auditory canal was completely absent. The middle ear cavity was occupied by a solid plate of bone forming the atresia plate. The stapedial footplate could however be seen at the oval window region (Fig. 3).

Histologic Characteristics of the Inner Ear. Postmortem and artifactual changes were minimal, allowing for good interpretation. The otic capsule of the cochlea showed normal bony pattern but the contour was irregular, presenting a widened basilar coil which abruptly narrowed down distally. The modiolus appeared stunted with the bulk of it stopping short at the distal margin of the basilar coil. The interscalar septum between the basilar coil and the middle coil was partially deficient, producing scala communis commonly seen in the Mondini defect (Fig. 4). Very few spiral ganglion cells could be seen in the modiolus. Nerve fibers were scanty in Rosenthal's canals; loose strands of connective tissue replaced them. The Reissner's membrane appeared wavy and redundant in most sections. The orifice of the cochlear aqueduct was widened. The tectorial membrane appeared normal, exhibiting Hensen's stripe. The stria vascularis showed areas of intensely basophilic staining chiefly in the middle coil with complete absence of cytologic characteristics (Fig. 5). The basophilic material proved to be PAS positive suggesting possible hyaline degeneration. This finding has been previously described by Schuknecht in cases of atrophy of stria vascularis manifesting in sudden sensorineural hearing loss.[1]

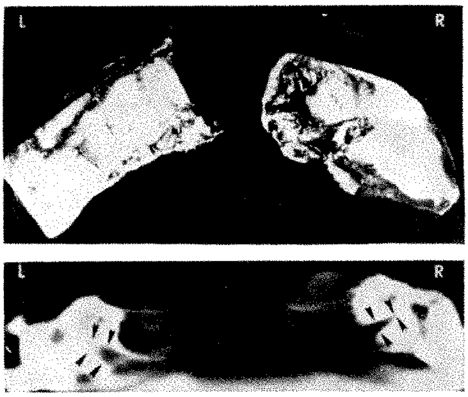

Fig. 2. Tomogram of the petrous bones showing the narrow triangular shaped internal auditory meatus on the right side.

The vestibular system presented normal structural anatomy of the utricle, saccule, and the canals. The only abnormality to be seen was in the endolymphatic duct and sac and in the number of Scarpa's ganglion cell population. The lining epithelium of the

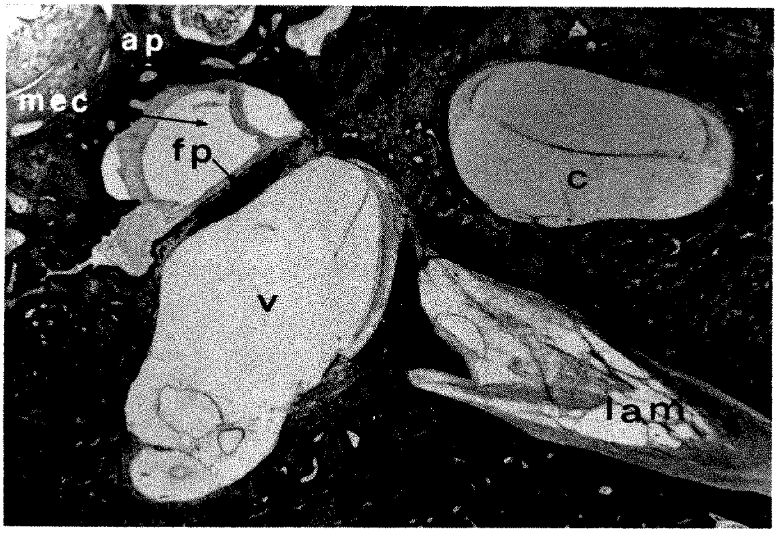

Fig. 3. Horizontal section of the right temporal bone at the level of the stapedial foot plate showing the tiny middle ear cavity with no structures in it. There is a thick atresia plate closing off the cavity laterally. IAM - Internal auditory meatus; C - Basilar coil; V - Vestibule; FP - Footplate of stapes; AP - Atresia plate; MEC - Middle ear cavity.

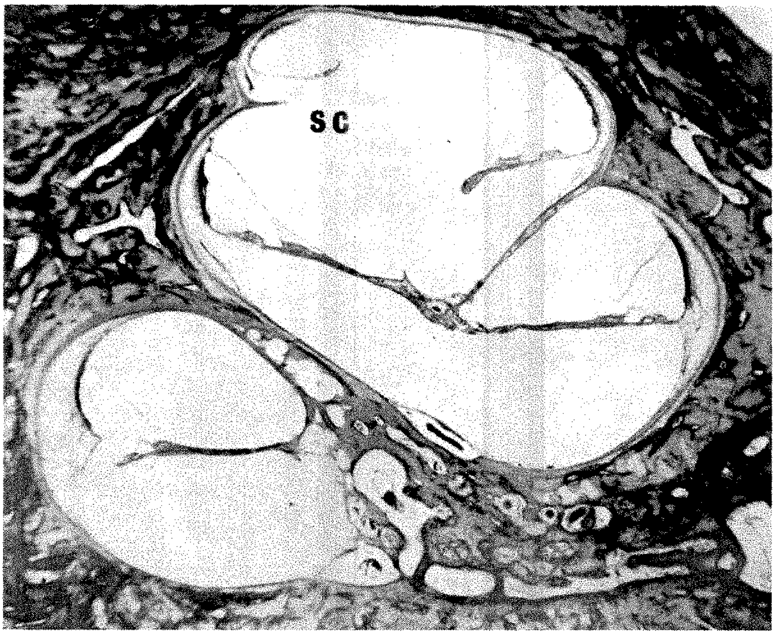

Fig. 4. Section of right cochlea showing absence of the bony septum between the middle and apical coils. SC - Scala communis.

endolymphatic duct was flattened. Dense fibrosis of subepithelial tissue was seen with relative sparsity of vasculature. Normal rugosity was totally absent with interluminal adhesions between the opposite walls.

Very few Scarpa's ganglion cells could be seen in the internal auditory canal. There was a corresponding decrease in the number of vestibular nerve fibers.

Facial Nerve. Motor facial nerve

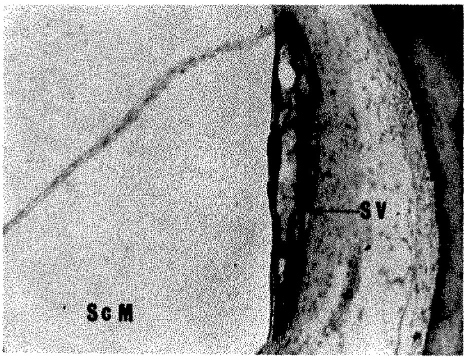

Fig. 5. High power view of the lateral wall of the middle coil of the right cochlea. Note the intense basophilic staining of the stria vascularis. ScM - Scala media; SV - Stria vascularis.

fibers were nonexistent. What lay in the furrow representing superior dehiscence of the petrous bone was a mass of nerve tissue exhibiting pseudounipolar ganglion cells possibly belonging to the geniculate ganglion. At the lateral end of the canal, the mass of nerve fibers turned forward, continuing as the greater petrosal nerve in the direction of the hiatus facialis. Another nerve emerged from the middle of the anterior wall of the canal, taking a devious route over the bony cochlea in an anterior direction. This could represent either the lesser petrosal nerve or the chorda tympani nerve given off anomalously in the internal auditory meatus.

The left temporal bone showed normal features providing excellent contrast for study.

DISCUSSION

Hemifacial microsomia relates to anomalies of the first and second branchial arches. It is characterized by varying degrees of underdevelopment of craniofacial structures such as the ear, mandible, zygoma, pterygoid processes, mastoid and tympanic temporal bones, maxilla, muscles of mastication, facial nerve and muscles, tongue and parotid gland. An excellent description of this entity can be found in the paper by Converse et al.[2] Several names have been designated to this syndrome depending on the extent of the involvement of the different structures mentioned. Names such as otomandibular dysostosis, unilateral facial agenesis, unilateral intrauterine facial necrosis are all found in the literature. A variant of this entity exhibiting vertebral and ophthalmic anomalies has been called "oculo-auriculo-vertebral dysplasia" or Goldenhar-Gorlin syndrome. Careful analysis of several cases of this broad syndrome complex of hemifacial microsomia has failed to reveal any evidence that it is inherited, unlike the well-documented Treacher-Collins syndrome, which is a hereditary disorder. The causative factor must therefore be a noxious environmental influence operating at a particular stage in the development. The malformations in such disorders have been explained on the basis of the involvement of the visceral mesoblast (which induces the nervous system and its protective tissues) in the developing embryo during the first trimester of pregnancy.

Our case fits the description of oculo-auriculo-vertebral dysplasia in that it represents vertebral anomalies and anophthalmia in addition to the hemifacial hypoplasia. The reader is referred to the article by Gorlin et al[3] on this subject. The profusion of names in this syndrome complex would lead one to believe that the clinical cases described under the headings of oculo-auriculo-vertebral dysplasia, hemifacial microsomia and branchial arch syndrome are essentially part of the same clinical entity. However, these terms by themselves do not encompass descriptively all of the clinical features and varieties of combinations that can be seen and therefore it may be justifiable to use the general eponym of Goldenhar-Gorlin syndrome.

Histologic Characteristics. Our case presents hypoplasia of the petrous bone and the ear structures in a patient with hemifacial microsomia. Clefts are seen in the petrous bone representing an open internal acoustic meatus and common chamber in the cochlea. Neural components including ganglion cells and nerve fibers are either reduced or absent. The picture is that of underdevelopment resulting in hypoplasia of the bony structures and the neural components conforming to the hypoplasia of the facial structures on the same side. It is microsomia of the right half of the face and adjacent skull base which leads one to assume the presence of an organizational defect in the developing embryo over a long period of time. One could speculate on the time of such environmental influence affecting the embryo. In our case the association of the cleft palate and ventricular septal defect would indicate that the damage occurred some time between the fourth and sixth week of embryonic life.

Lindsay[4] described a case involving absent right mandible and atretic right ear associated with cervical vertebral anomalies and considered it as a variant of Treacher-Collins syndrome. There were dysplastic changes noted in the inner ear structures. This case could possibly come under Goldenhar-Gorlin syndrome.

The association of branchial arch anomaly with otic capsule anomaly is not uncommon. Naunton and Valvassori[5] in 1968 reported an association of atresia and inner ear anomalies in 12% of their 66 cases. Frey[6] described 16 cases with inner ear anomalies; 14 of which had associated branchial arch anomalies. Diagnosis in these instances were made in the living with the help of petrous bone tomography.

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STUDY OF 100 PATIENTS WITH BILATERAL SENSORINEURAL HEARING LOSS FOR LIPID ABNORMALITIES

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SUMMARY — One hundred persons were selected from our audiology records who showed at least 20 dB bilateral sensorineural hearing loss. The number 100 was picked for an adequate statistical analysis. The patients were taken from the chart files which are filed in chronological order. Letters were mailed with instructions for fasting 14 hours prior to testing except for the consumption of water. On presentation, a history was taken for diabetes, height and weight, and the blood pressure was recorded. The blood samples were drawn in clot tubes and taken to a commercial laboratory for overnight refrigeration and testing of the serum. Testing included observation of serum for massive chylomicronemia, triglycerides, cholesterol and lipoprotein electrophoresis (by the cellulose acetate method). Lipoprotein testing results showed 12 patients with Type II A or II B and 8 patients with Type IV abnormalities. No Types I, III or V were found. These 20 patients represent a lower number of hyperlipoproteinemic patients than would be expected in the general population.

A relationship between sensorineural hearing loss and hyperlipoproteinemia has been suggested by Spencer.[1,2] Four hundred forty-four cases of sensorineural hearing loss and/or vestibular symptoms were correlated with the results of lipoprotein phenotyping. Of these, 46.6% were found to have hyperlipoproteinemias and 10.3% were borderline abnormal.

Rosen and Olin related hearing loss to coronary artery disease in populations with a high incidence of atherosclerosis and high dietary intake of saturated fats.[3] A positive correlation between high cholesterol levels and loss of hearing was presented. In addition, Rosen has presented several epidemiologic studies to support the relationship between abnormal dietary lipids and their vascular and otologic effects.[3-5]

A more modest relationship between serum lipoprotein phenotypes and extra-high frequency hearing acuity has been reported.[6] Nomura and Hiraide reported the presence of cholesterol deposits in the basilar membrane, concluding that it was a type of presbyacusis pathology.[7] In a review of sudden deafness, Jaffe implicated intravascular thrombosis in 11 of 40 cases. No mention was made of lipoprotein phenotyping.[8] The suggestion has been made that the coagulation properties of platelets are sensitized to epinephrine by hyperlipoproteinemia and may result in intravascular thrombosis.[9]

Apart from these efforts, specific attention to sensorineural hearing loss and primary hyperlipoproteinemia has been lacking. The primary hyperlipoproteinemias are diseases which manifest themselves as increased levels of specifically defined lipoprotein fractions. These are genetic diseases phenotypically expressing themselves as well defined clinical syndromes.

Frederickson and Lees' classification of the hyperlipoproteinemias, though considerably revised, remains the basis of reference for these disorders.[10] Hyperlipoproteinemia may reveal itself as a primary increase in plasma concentrations of lipoproteins or as a secondary elevation occurring in unrelated diseases. Hypothyroidism, alcoholism,

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Presented at the meeting of the American Neurotology Society, Boston, Massachusetts, May 11, 1977.

TABLE 1. VARIABLES INVOLVED IN PHENOTYPING LIPOPROTEINEMIAS OTHER THAN CHOLESTEROL AND TRIGLYCERIDES

- Chylomicrons (visible particles in lymph 1μ or less after feeding fats)
  - Triglycerides primarily
  - Protein 2-3%
  - Cholesterol (small amounts)
- Alpha lipoprotein — very high density lipoproteins
  - Protein 45-55%
  - Phospholipid 30%
  - Cholesterol 18%
  - Triglyceride (small amounts)
- Beta lipoproteins
  - Protein 20-25%
  - Phospholipid 22%
  - Cholesterol 43%
  - Triglyceride 10%
- Pre-Beta lipoproteins — very low density lipoproteins
  - Protein 15-20%
  - Phospholipid 20%
  - Cholesterol 35%
  - Triglyceride 25-30%

biliary cirrhosis, pancreatitis, nephrosis, uncontrolled diabetes mellitus and ketoacidosis have been associated with increased plasma lipoprotein concentrations. The collaborating determination of the different lipoprotein elevations reveals the phenotype. It should be realized however, that genetically different hyperlipemic diseases may present in patients with similar phenotypes.[11]

Screening laboratory tests will demonstrate fasting plasma triglyceride and cholesterol values. Large increases in triglycerides might indicate a Type IV elevation of very low density lipoproteins (VLD) or the rare association with a Type I primary hyperchylomicronemia. Increased cholesterol levels might indicate a Type IIa low density (LD) lipoproteinemia. Dual elevations in both cholesterol and triglycerides may indicate a Type IIb or Type III lipoproteinemia.

Lipoprotein phenotyping defines five phenotypes using six variables. These variables include chylomicrons, alpha lipoprotein, beta lipoprotein, pre-beta lipoprotein, cholesterol and triglycerides. While cholesterol and triglycerides are familiar terms the others may not be as well known (Table 1).

Familial hyperchylomicronemia or Type I phenotype is thought to be due to a deficiency that prevents the breakdown of chylomicrons into smaller particles. A large creamy layer on spun plasma or in serum, with an improvement on restriction of fats is virtually diagnostic (Table 2).

Familial hyper beta-lipoproteinemia or Type IIa hypercholesterolemia is the most clearly defined lipoproteinemia. Premature coronary arteriosclerosis disease and increased incidence of cerebrovascular disease are present.

Combined hyperlipoproteinemia, or Type IIb, is the most common primary hyperlipoproteinemia.[12,13] Elevation of pre-beta (LD) and beta lipoprotein (V-LD) are present. These patients have an increased incidence of coronary ar-

TABLE 2. PHENOTYPES OF HYPERLIPOPROTEINEMIA

Type	*Chylomicrons*	*Pre-Beta Lipoprotein*	*Beta Lipoprotein*	*Triglycerides*	*Cholesterol*
I	†	N	N	†	N to ††
IIa	N	N	‡	N to ‡	†
IIb	N	‡	‡	†	†
III*	N	‡	††	Variable	Variable
IV	N	‡	N	†	N to ‡
V**	‡	‡	N	‡	‡

*Abnormal staining Beta band.
**V = I & IV.
N - Normal; † - Markedly elevated; †† - Mildly elevated; ‡ - Moderately elevated.

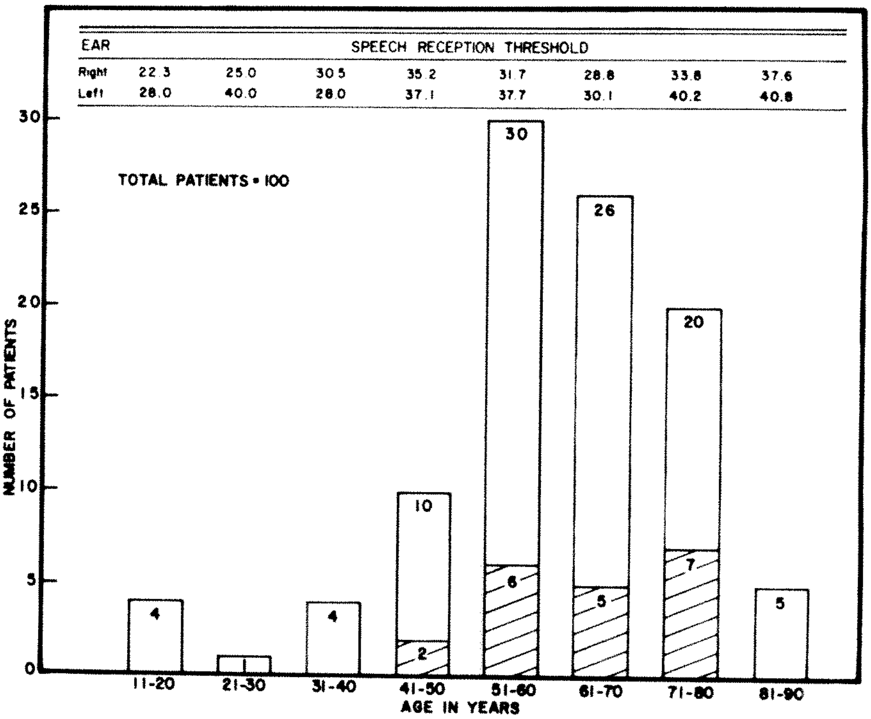

Fig. 1. Bar graph showing distribution of the 100 patients as to age. Cross matching indicates number in each group with hyperlipoproteinemia. The average speech reception threshold for each group is at the top of the illustration.

tery disease.[12,14] Diabetes mellitus is also frequently present.

Type III or broad beta lipoproteinemia presents as an abnormal complex of low density lipoproteins and triglycerides. These is some evidence that this represents an inability to breakdown the pre-beta lipoproteins.

Familial hyper pre-beta lipoproteinemia or Type IV shows hypertriglyceridemia with elevated cholesterol levels. Premature atherosclerosis with coronary artery disease and stroke are commonly present. Diabetes may be present in approximately 50% or greater.

Type V syndrome patients present with a mixture of the findings of Types I and IV.

PRESENT STUDY

Persons were added to the audiologic records previously mentioned in a preliminary analysis by Lowry.[15] A significant sensorineural hearing loss was present. One hundred patients were picked for statistical analysis. These patients were taken from the chart files which are assembled in chronologic order. Letters were mailed with instructions for fasting 14 hours prior to the testing except for the consumption of water. On presentation a history was taken for diabetes, height and weight; and blood pressure was recorded. The blood samples were sent to a commercial laboratory for overnight refrigeration and testing of serum.

Testing included:

1. Observation of serum for massive chylomicronemia.
2. Triglycerides.
3. Cholesterol.
4. Lipoprotein electrophoresis (by cellulose acetate phthalate method).

This laboratory claims that approximately 90% of the results using this method are consistent with the clinical diagnosis.[16]

RESULTS

Forty-nine percent were males and 51% were females. Twenty percent of the studied population had lipoprotein abnormalities. Eight percent had positive or borderline diabetes mellitus as measured by the 5-hour GTT. Twenty cases or 20% have been diagnosed as having both hyperlipoproteinemia and sensorineural hearing loss. Of this group, 12 patients exhibited Type II (Type IIa or IIb) and 8 patients were Type IV. This represents 12 and 8% of the patient population respectively. No Types I, III or V were encountered.

The greatest number of patients tested fell into the 51-60-year-old group. Age groups 60-70 and 71-80 were the next greatest (Fig. 1). The incidence of patients with sensorineural hearing loss and lipoprotein abnormalities was the highest in the 71-80-year-olds with the 51-60 group having the next greatest incidence. The average speech reception thresholds are demonstrated in Figure 1.

DISCUSSION

The auditory system is very susceptible to vascular insufficiency.[17] The basal or high frequency end of the cochlea is especially affected. This occurs even though the auditory system has the greatest vascularity of all central nervous system parts.[18] The metabolic rate of an area is related to the degree of vascularity with which it is supplied. Disorders of metabolism would place these highly susceptible areas at risk. Disorders of the physiologic control of lipoprotein metabolism may affect these areas significantly.

While the internal auditory and cochlear arteries are probably not involved directly by the atherosclerosis resulting from hyperlipoproteinemias, they may still contribute to adverse changes in the areas they supply. The alterations caused by atherosclerotic change may be ischemic or resemble the changes seen in similar metabolic disturbances of the ocular fundus.[2]

Very low density lipoproteins and LD lipoproteins are the most important factors in the pathogenesis of atherosclerosis. It has become established that these fractions accumulate, in the early stages of the disease, within the arterial intima.[19]

The prevalence of primary hyperlipoproteinemia within the general population has not been well-determined.[1] In a study of blood donors in Albany, New York, no Type I or Type V hyperlipoproteinemias were demonstrated.[20] There were 26% males and 8% females with Type IV hyperlipoproteinemias. There were 8.7% and 10.4% Type II hyperlipoproteinemias. Diabetes and hypertensives with greater than 200 mm Hg systolic pressure were not accepted as blood donors. These was an overnight fast. The results of this study are at variance with the findings of Spencer and underline the uncertainty about the prevalence of these disorders.[1]

The 100 patients presented here represent a lower number of hyperlipoproteinemic patients that would be expected in the general population. In addition they represent a significantly smaller percent of patients with associated sensorineural hearing loss and hyperlipoproteinemia than previously reported.[1,2] Analysis of a population of hyperlipemic patients with respect to associated hearing loss may prove valuable in further assessing this relationship. The occurrence of increased numbers of VLD and LD lipoproteinemias with older age groups is not unexpected.[21] Hyperlipemic patients have been detected by observing hearing losses at very high frequencies (especially 14 kHz.) These correlations represent a definite but modest relationship at best.[6] Hypercoagulation secondary to platelet abnormalities in hyperlipoproteinemia Type IIa may be a significant etiologic factor in hearing loss.

SUMMARY

One hundred patients with sensorineural hearing loss were tested for hyperlipoproteinemia. They showed a lesser number of patients with lipoprotein abnormalities than one would expect from the reported prevalence for the general population.

Comparison of hearing loss in these patients showed a substantially greater loss than hearing loss expected with presbyacusis alone.[22]

The possible relationship between the disordered metabolism of lipoproteins and hearing loss deserves further study.

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NECROTIZING SIALOMETAPLASIA

A SELF-LIMITED PSEUDOTUMORAL PALATAL ULCER

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SUMMARY — Necrotizing sialometaplasia of the palate, an enigmatic pseudomalignant penetrating ulcer, is a benign lesion which heals spontaneously in three to ten weeks. Relative painlessness contributes to patient delay in seeking medical attention, and suggests that many cases are subclinical. Clinically, the patient age group and morbid gross appearance mimic malignant palatal tumors. Lack of awareness of this entity has led to the misdiagnosis of carcinoma in several previous cases. However, the histopathologic features of sialadenitis, focal lobular necrosis with mucosal ulceration and glandular squamous metaplasia, are distinctly benign. A typical case and literature review are presented.

Necrotizing sialometaplasia is characterized by a self-limited hard palatal ulcer. Despite the alarming clinical appearance which simulates palatal carcinoma, the histologic features are benign. Lobular necrosis secondary to sialadenitis with consequent mucosal ulceration and exuberant squamous metaplasia of acini and ducts have been misinterpreted as carcinoma in at least 6 of the previous 15 cases reported.[1-5] Recognition of this entity is essential to obviate unwarranted aggressive therapeutic measures.

CASE REPORT

Over a three-day period, a 41-year-old Caucasian male western artist noted progressive palatal discomfort and localized swelling. One month previously, he was successfully treated for beta hemolytic streptococcal pharyngitis. He denied the habit of holding brush ends in his mouth or any recent trauma. He was routinely exposed to varnish, which he sprayed on his canvases, and smoked two to three cigars a day. There was no history of alcohol abuse or diabetes mellitus. Hydralazine and propanolol were administered for moderate hypertension. Physical examination disclosed a discrete erythematous tender swelling beneath an intact mucosa on the posterior hard palate just left of the midline. Cultures yielded normal oral flora. At re-examination four days later, there was a 3 cm ulcer which was minimally tender (Fig. 1). The mucosal borders were irregular, erythematous and slightly overhanging. Repeat cultures were negative. Palatal x-rays revealed no bony defect. Incisional biopsy was performed and the patient was placed on broad-spectrum antibiotics. The lesion healed in four weeks without complications.

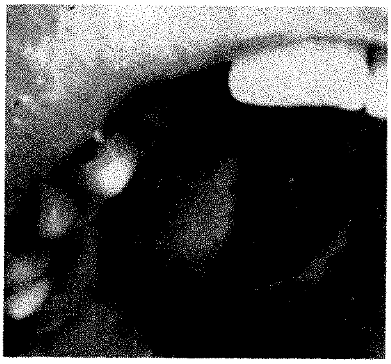

Fig. 1. Hard palatal ulceration with irregular erythematous margins.

HISTOPATHOLOGIC FINDINGS

The ulcer crater was filled with inflamed necrotic debris and partially lined by granulation tissue. Lobules of the minor salivary glands closest to the crater had undergone partial infarction with some coalescence of mucin (Fig. 2). Despite the inflammatory changes, an orderly glandular architecture was maintained. Acini and ducts remote from the ulcer had undergone squamous metaplasia and hyperplasia (Fig. 3).

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TABLE 1. COMPARATIVE DIFFERENTIAL CLINICAL FEATURES

	Necrotizing Sialometaplasia	*Benign Glandular[8] Palatal Tumor*	*Malignant Glandular[8] Palatal Tumor*
Average age (yr)	45	49	51
Range (yr)	23-66	10-82	20-79
Pain (%)	33	5	30
Ulceration (%)	94	11	32
Average size of lesion (cm)	1.6	2.0	2.9

No vasculitis, thrombosis, granuloma or micro-organisms were seen. The mucosal ulcer edge exhibited pseudoepitheliomatous hyperplasia.

DISCUSSION

The differential diagnosis of deep palatal ulceration is relatively limited. Traumatic injury, opportunistic infections and lethal midline granuloma are etiologies easily determined by clinical history and appropriate laboratory and radiographic studies. In necrotizing sialometaplasia of the hard palate, bone is usually intact; however, faint radiolucency has been seen in two cases.[1]

The discrete and painless early palatal lesion most often suggests neoplasia of a minor salivary gland. Minor salivary gland tumor of the palate is uncommon; only 120 cases were seen at the Mayo Clinic during a 20-year-period.[6] Of these cases, half were benign pleomorphic adenoma. The malignant types were adenoid cystic or mucoepidermoid carcinoma. Table 1 compares the clinical findings in necrotizing sialometaplasia and minor salivary gland tumor; ulceration appears more

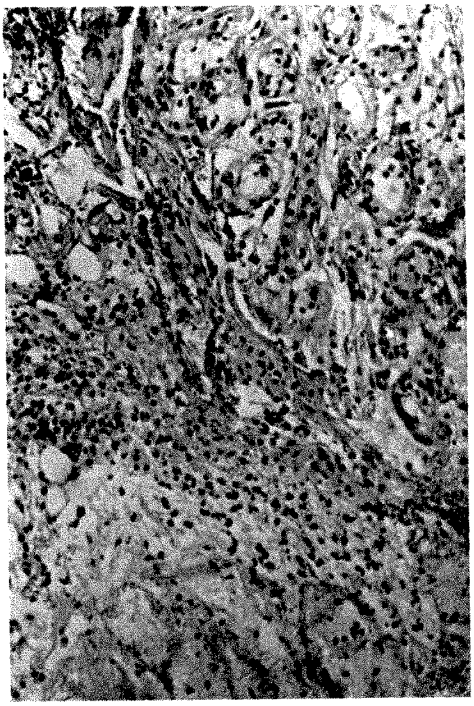

Fig. 2. Necrotic minor salivary gland near ulcer bed. Despite some mucus coalescence and inflammation changes, there is preservation of acinar architecture (H. & E., X 40).

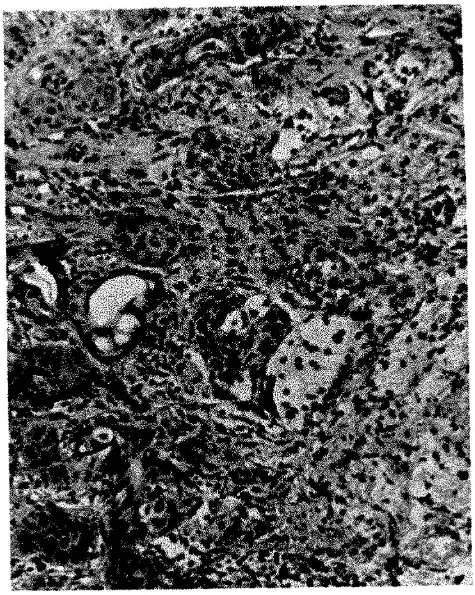

Fig. 3. Exuberant squamous metaplasia of acini and mucin coalescence are features that have been mistaken for carcinoma (H. & E., X 40).

TABLE 2. DATA SUMMARY OF REPORTED CASES (N = 16)

	No.
Age	
20-29	3
30-39	1
40-49	6
50-59	5
60+	1
Av. 44.9	
Sex	
Male	11
Female	5
Race	
Caucasian	10
Negro	5
Location	
Hard Palate	14
Soft Palate	2
Laterality	
Left side alone	6
Right side alone	1
Bilateral	3
Largest dimension of ulcer (cm)	
1.0 or less	5
1-2	4
3 or more	3
Misdiagnosis	
Mucoepidermoid carcinoma	4
Squamous cell carcinoma	2
Surgical management	
Incisional biopsy	9
Complete excision	3
Complete healing interval	
3-4 weeks	2
8-10 weeks	3
No evidence of recurrent disease	
6 mo or less	4
1-4 yr	4
6+ yr	3

frequently in necrotizing sialometaplasia. Some patients with necrotizing sialometaplasia have had referred pain to the ear[3] or pharynx,[1] while others had sensations of numbness, fullness or "loosening."[2] Data summarizing the 16 reported cases are presented in Table 2.

Incisional biopsy for diagnosis is sufficient surgery for necrotizing sialometaplasia since it is a self-healing benign entity. By contrast, total excision is required for tumor. Therefore, intraoperative frozen section is helpful in operative management provided proper diagnosis is made. Unfortunately, several cases were histologically interpreted as cancer.

The etiology of necrotizing metaplasia is unclear. Usually there were no systemic symptoms. One of the original cases had "gas fume" exposure.[1] Our patient regularly used varnish and paint thinners. Other reported associated factors, which appear to be coincidental, include dentures, alcoholism, heavy smoking, arteriosclerosis and diabetes mellitus. Trauma appears to be the factor most likely to produce the pathogenic cascade of findings. A focal lobular sialadenitis has been observed in five resected major salivary glands by Batsakis.[7] In each, there was a prior diagnostic biopsy. This change has not been noted in other minor salivary glands.[5] However, it may be that Batsakis' findings represent the earliest histologic changes of necrotizing sialometaplasia. To speculate further, it is possible many palatal cases never reach the full-blown lesion with ulceration. This supposition plus the relative painlessness and the self-healing nature of the entity may contribute to under-reporting. If necrotizing sialometaplasia is more common than these few cases would imply, it is most important for those involved with oral cancer management to become familiar with it.

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MAJOR IMMUNOGLOBULIN RATIOS IN CARCINOMA OF THE HEAD AND NECK

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SUMMARY — Serum immunoglobulin A (IgA), immunoglobulin G (IgG), and immunoglobulin M (IgM) levels were determined on 245 patients with carcinoma of the head and neck and on 92 controls. Ratios of these levels were calculated for each subject. The patients with cancer demonstrated elevated serum IgA levels ($P < .0001$) and elevated IgA/IgM and IgA/IgG ratios ($P < .05$). No differences were noted when the IgM/IgG ratios were compared between the cancer and the control groups. These observations are offered as evidence that previously reported elevations of serum IgA levels in patients with carcinoma of the head and neck are not merely an index of nonspecific increased immunoglobulin production in these patients.

Recently the immune system in patients with carcinoma of the head and neck has received a great deal of attention. It has been reported that abnormalities of the cellular immune system are seen more frequently in patients with carcinoma involving other sites of the body.[1] Along with impaired delayed hypersensitivity,[2-4] T-cell deficiencies have also been reported.[5-7] Abnormalities of the humoral immune system have also been noted in this group of patients. Elevated levels of serum immunoglobulin A (IgA) have been reported in carcinoma of the oral cavity,[8,9] nasopharynx,[10] and head and neck.[11] Elevated salivary IgA levels have been reported in patients with oropharyngeal and bronchopulmonary carcinoma.[12] Epstein-Barr virus-specific IgA serum antibodies have also been noted to be elevated in patients with carcinoma of the nasopharynx.[13]

This study was designed to determine if the elevated levels of IgA seen in carcinoma of the head and neck represent a specific immunoglobulin elevation, or represent an index of diffuse immunoglobulin production in response to chronic stimulation by tumor associated antigens.

METHODS AND MATERIALS

Patients. Blood samples were collected on 245 patients as they presented in the Department of Otolaryngology and Maxillofacial Surgery, Iowa City, with carcinoma of the head and neck. The serum was separated and frozen at −20 C until immunoglobulin determinations were performed at a later date. Control blood samples were collected from 92 blood bank volunteers over the age of 40.

Methods. Quantitative determinations of immunoglobulin A (IgA), immunoglobulin M (IgM), and immunoglobulin G (IgG) were carried out by the radial immunodiffusion method of Mancini et al.[14] Commercially prepared radial immunodiffusion plates with standards were purchased from the Behring Diagnostics.* The plates and standards were stored at 4 C until use.

The diameter of each precipitin ring was measured to an accuracy of 0.1 mm using a calibrated magnifier and a dissection microscope. A 1:10 dilution of patient sera was made with 0.01 M phosphate buffered saline (pH = 7.3) if the observed concentrations of immunoglobulins exceeded the limits of the plate employed.

Ratios of immunoglobulin concentrations of each individual patient were calculated. Pa-

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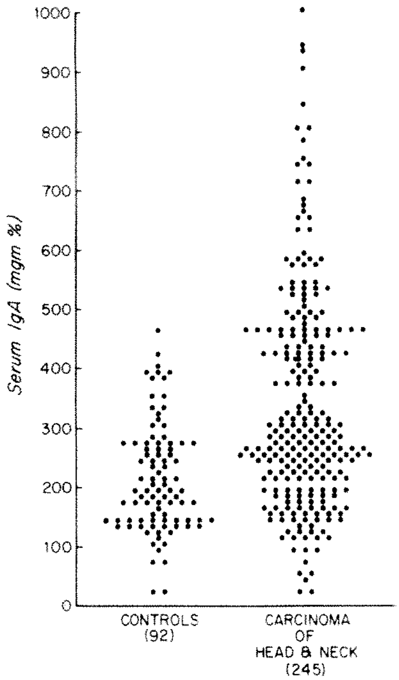

Fig. 1. Serum IgA in carcinoma of the head and neck.

tients are also being followed with repeated blood samples and clinical information on these patients is being collected.

RESULTS

Serum IgA levels ranged from 30 mg% to 1000 mg% in the patients with cancer; while the control group serum IgA levels ranged from 30 mg% to 463 mg% (Fig. 1). Normal serum IgA levels have been reported to range between 55 mg% to 486 mg%[15] and 66 mg% to 344 mg%[16] by other authors. Sixty patients with carcinoma (24.5%) had serum IgA levels >450 mg%; whereas, only one control (1.1%) demonstrated levels greater than this value ($P < .0001$; X^2 test).

Serum IgA/IgM ratios were calculated for each patient with carcinoma and ranged from 0.1 to 28.7, with a median of 2.1. The ratios ranged from 0.1 to 9.5 in the control group, with a median of 1.4 (Fig. 2). Fifty-one (20.8%) of the patients with carcinoma had an IgA/IgM ratio of 4.0 or greater; while only eight (8.7%) of the control group demonstrated an IgA/IgM ratio of at least 4.0 (Table 1). Patients with carcinoma of the head and neck demonstrate an elevated IgA/IgM ratio over controls ($P < .05$; Bonferroni Multiple Comparisons).

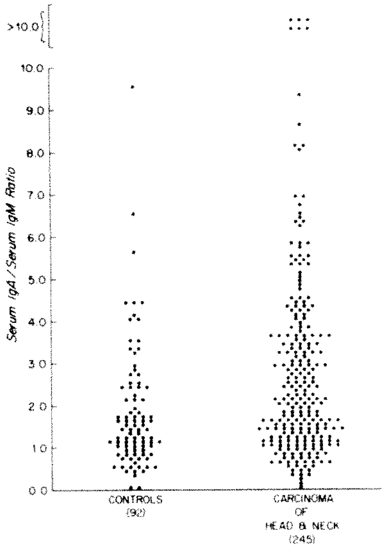

Fig. 2. Serum IgA/IgM ratios in patients with carcinoma versus controls.

Serum IgA/IgG ratios ranged from 0.01 to 1.07 in the patients with carcinoma, with a median of 0.24. Controls ranged from 0.01 to 0.57, with a median of 0.16 (Fig. 3). Other authors have reported similar IgA/IgG ratios for normal controls to be 0.15 in females and 0.18 in males.[8] One hundred and fifty-nine (64.9%) of the patients with carcinoma demonstrated a ratio of greater than 0.20; while only 33 (36.3%) of the control group demonstrated ratios

TABLE 1. IgA/IgM RATIOS IN PATIENTS WITH CARCINOMA OF THE HEAD AND NECK

IgA/IgM Ratio	*Controls (92)*	*Patients with Ca of Head and Neck (245)*
< 2.0	64 (69.6%)	114 (46.5%)
> 2.0	28 (30.4%)	131 (53.5%)
> 4.0	8 (8.7%)	51 (20.8%)
> 6.0	2 (2.2%)	18 (7.3%)
>10.0	0 (0.0%)	6 (2.4%)

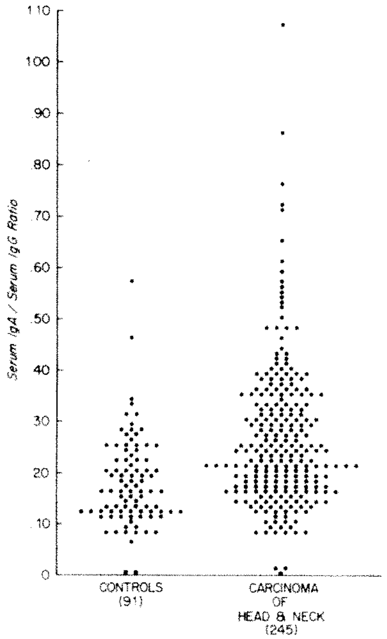

Fig. 3. Serum IgA/IgG ratios in patients with carcinoma versus controls.

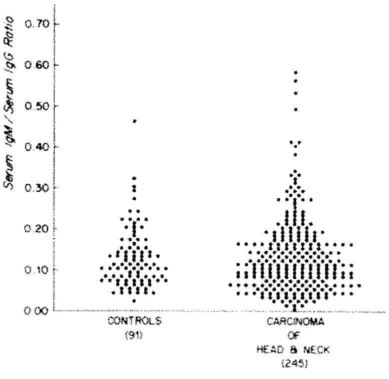

Fig. 4. Serum IgM/IgG ratios in patients with carcinoma versus controls.

this high (Table 2). Patients with carcinoma of the head and neck have a higher IgA/IgG ratio than controls (*P* <.05); Bonferroni Multiple Comparisons test).

IgM/IgG ratios were not significantly different between the two groups. Both had median ratios of 0.11 (Fig. 4).

DISCUSSION

Several laboratories[8-11] have now reported elevated levels of serum IgA in carcinoma of the head and neck. We have shown that these elevated IgA levels are not an index of diffuse immunoglobulin production; but rather they represent a specific elevation of IgA. When IgA is compared to the levels of IgM and IgG, elevated ratios have been documented. Whether these ratios represent a factor in the etiology of carcinoma, a response to the carcinoma, or an immunopathologic phenomenon unrelated to the presence of carcinoma is yet to be established.

TABLE 2. IgA/IgG RATIOS IN PATIENTS WITH CARCINOMA OF THE HEAD AND NECK

*IgA/IgG Ratio**	*Controls (91)*	*Patients with Ca of Head and Neck (245)*
< 0.2	58 (63.7%)	86 (35.1%)
> 0.2	33 (36.3%)	159 (64.9%)
> 0.4	2 (2.2%)	30 (12.2%)
> 0.6	0 (0.0%)	7 (2.8%)
> 1.0	0 (0.0%)	1 (0.04%)

*IgG levels were determined on 91 controls.

Several facets of the immunoglobulin A system are becoming apparent. Salivary IgA has been noted to have a neutralizing activity against viruses,[17] and elevated levels of IgA specific for the Epstein-Barr virus appear to have prognostic implications in patients with carcinoma of the nasopharynx.[13]

The association between the development of autoimmune disease and IgA deficiency has led Good and Rodey to propose that a role of the IgA system may be to stand as a barrier against certain antigens and render them ineffective as antigenic stimuli.[18] It seems reasonable to propose that if such were the case, excess IgA may combine with tumor associated antigens; and thereby, render them ineffective as antigenic stimuli. Indeed, we have preliminary data which suggests that the higher the serum IgA level the poorer the prognosis in patients with carcinoma of the head and neck.

This study is presented as evidence to support the observation that serum IgA levels are elevated in certain patients with carcinoma of the head and neck. Elevated levels of IgG and IgM are not seen in as great a frequency; and, therefore, IgA/IgM and IgA/IgG ratios are noted to be increased in patients with carcinoma. This observation suggests that the observed elevated IgA levels are not merely laboratory artifacts, as may be seen in the dehydrated patient. The immunoglobulin A system appears to be a fruitful area for further investigation

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DYSPLASTIC EPITHELIAL CHANGES IN NASAL POLYPS

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SUMMARY — In 33 patients undergoing nasal polypectomy, severely dysplastic or intraepithelial malignancy was observed focally in the surface lining of these polyps. Follow-up on 29 of these patients showed that the changes did not recur or progress to invasive tumor, and that local excision was curative. Investigations as to the possible causation of such changes failed to provide any answers. Other hypotheses in relation to the pathogenesis and significance of these changes are put forward.

The reporting of epithelial changes as premalignant or "borderline" malignant by the histopathologist is a source of frustration and anxiety in the planning of the surgical treatment of the patients in question; the multiplicity of apparently synonymous pathological terms, such as dysplasia, atypical hyperplasia and atypism which are also often used in this context, adds further to the confusion. Where such changes have progressed to actual intraepithelial malignancy (carcinoma in situ), management may be even more problematic.

A site where fortunately such pathological changes are only met with infrequently is the nasal respiratory mucosa. This paper reports on a study of a series of cases in which severely dysplastic or carcinoma in situ changes were diagnosed in the epithelium overlying simple nasal mucous polyps. All these patients were followed up clinically over a period of years in an attempt at assessing the significance, prognosis and pathogenesis of such pathological processes at this site.

METHODS AND MATERIALS

Over the period 1964-1974 microscopic examination of surgically removed nasal polyps from 33 patients showed the presence of severe epithelial dysplasia or carcinoma in situ. These patients were treated at the Ear, Nose and Throat Hospital, and the ENT wards of the Western Infirmary, in Glasgow, Scotland. Over the same interval nasal polyps from 1,710 patients from the same hospital were examined microscopically (Fig. 1). Twenty-nine of the patients were male and four female; their ages ranged from 26 to 78 years with a mean of 52 years. The cases with dysplasia were evenly distributed over the period of the study.

Twenty-six of the patients were followed up for periods ranging from two to ten years with a mean follow-up of about six years. After that an initial pathological diagnosis was established in addition to regular clinical and rhinoscopic examination. Several of them were also subjected to further biopsies of their nasal epithelia or further removal of recurrent polyps; this material was also available for study. In the instance of the patients who had already been discharged from the outpatient clinics, the respective general practitioner was contacted and detailed inquiries about the patient's nasal condition were made.

All the histological material was stained by the ordinary H & E method after embedding of the formalin-fixed material in paraffin wax. Sections from different levels in the blocks were studied in order to exclude artifacts related to erroneous embedding of the specimen in wax, and any resultant "squint," oblique or tangential microtome sectioning.

To avoid misinterpretation in a study of this type it is essential to define exactly the terms employed, as certain minor nuances in terminology may exist. The definitions of the terms as used are tabulated:

Metaplasia. This transformation of one type of epithelium into another is present frequently as a squamous change of the respiratory pseudostratified columnar epithelium of the nasal polyps. This ranges from an increase in the thickness of the epithelium and a tendency to horizontal alignment and flattening of the component cells (the so-called "transitional epithelium" of the nose) to a typical squamous lining with a hyperchromatic basal layer, a "prickle" cell layer and a flattened superficial layer; actual keratinization is unusual in the nasal epithelium. This change is not to be considered in any way sinister although the dysplastic changes observed usually

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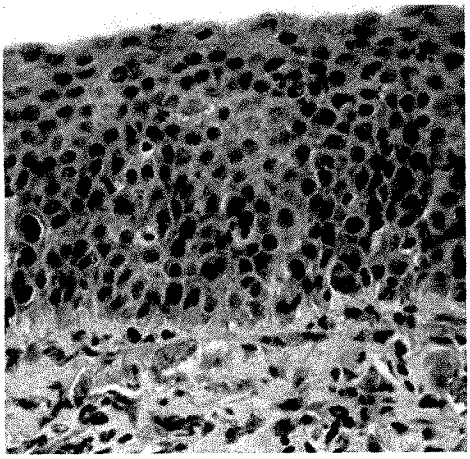

Fig. 1. Squamous metaplasia in the respiratory epithelium overlying a nasal polyp. (H & E, X300)

appeared at sites of preexisting squamous metaplasia (Fig. 1).

Dysplasia. The typical cytological features of the dysplastic epithelium are an increase in the number of epithelial cells (hyperplasia) and a disturbance in their maturation resulting in some loss of polarity; a tendency towards a surface-oriented maturation is still maintained to a varying extent. The component epithelial cells show irregularity and hyperchromicity of their nuclei; mitoses are no longer restricted to the basal layer and can be observed at all levels within the lining. The degree of dysplasia ranges from a mild form with a minimal polarity disturbance, to a severe form where there is complete disorganization of cellular polarization and a degree of dedifferentiation approximating intraepithelial malignant degeneration; hence the use of the term "premalignant" or "precancerous." Such degrees of dysplasia are still capable of reversal to less severe forms and to normality (Fig. 2). (The term "dysplasia" is often used synonymously with atypical epithelial hyperplasia or atypism.)

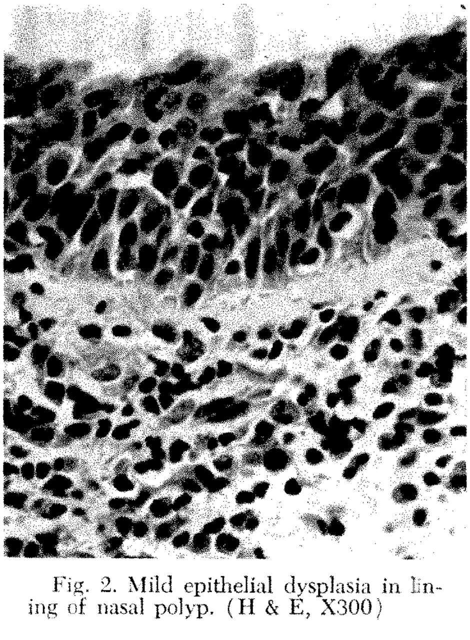

Fig. 2. Mild epithelial dysplasia in lining of nasal polyp. (H & E, X300)

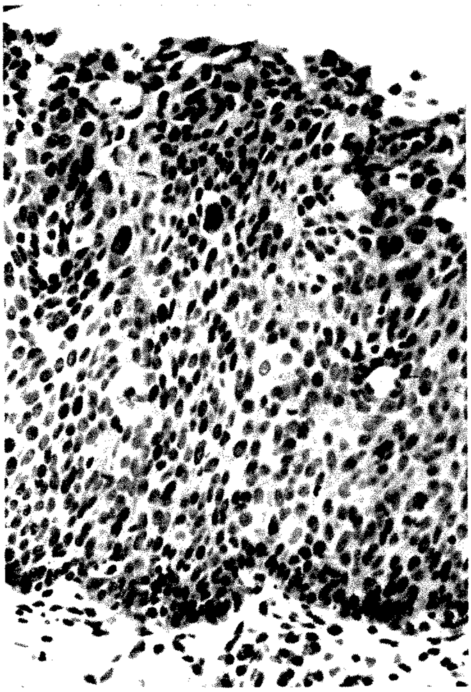

Fig. 3. Intraepithelial carcinomatous changes of the respiratory lining of a nasal polyp. (H & E, X300)

Carcinoma in situ (Intraepithelial Malignancy; Intraepithelial Carcinoma). The epithelial lining is totally replaced by cells showing all the cytological features of malignancy and which microscopically are indistinguishable from those of a frankly invasive carcinoma; the loss of stratification is complete with no residual polarity or differentiation at any level and no tendency towards a surface-directed maturation. The surface cells may be flattened but they still appear abnormal. The basement membrane is still intact and no stromal invasion has occurred. There is therefore a marked degree of intraepithelial cellular pleomorphism with an increase of the nuclear to cytoplasmic ratio, a loss of intracytoplasmic glycogen and the other features of cytoplasmic differentiation. Mitotic figures are frequently observed along the entire breadth of the lining; some of these may be bizarre with multipolar mitotic spindles; multinucleate and giant cell forms may also be present (Fig. 3).

All the biopsies included in this study fulfilled the above criteria in showing either a severe form of dysplasia or carcinoma in situ.

RESULTS

The atypical epithelial changes which this small group of nasal polyps showed were only focal in that only one tiny strip of the entire mucosal lining of the polyp was abnormal: this was never in excess of 0.1 cm and often much smaller. The mucosa in the immediate vicinity only showed squamous metaplasia or simply some increase in thickness. In only a small minority of these cases were the changes observed at more than one focus and the change was invariably unilateral.

The underlying edematous stroma of the polyp at the sites of atypical epithelium was not different from that of a typical nasal mucous polyp, and the inflammatory infiltrate present was not unusual in its quantity or cellular composition. None of the patients in whom subsequent nasal polypectomies or nasal biopsies were performed showed a recurrence of the change, and in no case did invasive tumor supercede.

The reasons why such a small and rather insignificant proportion of polyps should manifest atypical epithelial changes are not apparent from this study. The age distribution of these patients is identical to that of the whole cohort of patients seen over the same time interval with histologically "ordinary" polyps. No clues were forthcoming from the detailed investigation of the occupations of the patients under review; in particular there was no evidence that they were exposed in the course of their work to excessively dusty environments or to the inhalation of irritant fumes or gases and none of the patients was in any way connected with the timber or furniture industry. The spectrum of their smoking habits was also very broad with about half of the patients being nonsmokers. No hints were forthcoming from an analysis of their allergic histories. Only five patients (19%) admitted to any form of allergy, e.g., asthma, eczema: the nasal epithelial abnormality in the latter patients did not significantly differ in degree of severity from the rest of the group.

The duration of the history of the nasal disability elicited from the patients with dysplasia was also typical. In the majority of patients the symptoms extended over a number of years and in three cases exceeded ten years. Eight of the patients had undergone previous nasal polypectomies. There was again no correlation between the duration of the history and the severity of the dysplasia. No relationship to the forms of local or systemic mediation that the patient had applied could be established. At surgery no unusual features were recorded in either the gross appearances or the actual location of the polyps.

DISCUSSION

It is only very random samples of nasal polyps which show unusual features but this still justifies the histological examination of all such surgical specimens. The epithelial changes of severe dysplasia or intraepithelial carcinoma are disconcerting to the histopathologist at any site; on observing such changes in the nasal epithelium one can only transmit his anxiety to the clinician's judgment, applying similar caution in this instance, as that which would be favored for similar changes in other more familiar sites.

As histologically the changes of severe dysplasia merge into carcinoma in situ, cases showing either of the two changes were grouped and studied together. The first matter which requires consideration is terminology: the pathologist and the surgeon may not be using comparable vocabulary and the latter's reaction may be completely out of gear in relation to the level of suspicion which the biopsy report may or may not be trying to convey. Furthermore, minor variations in semantics do exist between different pathology departments and even between individual pathologists[1,2] and it is essential that the surgeon understands fully what his laboratory colleague is trying to state. On the other hand, the pathologist can only describe the changes which he observes in his microscope and attempt to interpret them by extrapolating to such relatively unfamiliar sites as the nasal mucosa, and data accumulated from the study of similar epithelial changes in the other anatomical locations where such abnormalities occur more frequently.

The most common site for such dysplastic changes is the squamocolumnar junction of the uterine cervix. Since the original description of atypical epithelial hyperplasia at this site by Schauenstein[3] and by Schiller,[4] large series of women with cervical dysplasia have been investigated at a number of centers[5] and it has been shown convincingly that this change is reversible, but, in its more severe varieties, may march on over a variable period of years to carcinoma in situ, and even invasive carcinoma.[6,7] Intraepithelial malignancy is also still potentially capable of regression, but is more likely to progress to invasive tumor. The capacity of reversal of this change is particularly surprising[8] as the epithelial cells in the preinvasive stage already exhibit all the morphological, biochemical, and chromosomal aberrations of infiltrating malignancy. Such studies have also shown that prognostically severe dysplasia and carcinoma in situ are identical.[9]

Comparable epithelial changes can be observed in the epidermis,[10] laryngeal mucosa,[11] and conjunctiva.[12] At the latter sites, as also in the cervix, the histopathologist can offer little assistance with prognosis: histology, cytology, and histochemistry do not supply any hints regarding in which direction a particular atypical epithelium will proceed. The prophetic-sounding and speculative terms "precancerous" and "premalignant" are therefore best abandoned unless they are endowed with a restrictive definition, mutually intelligible to surgeon and pathologist.

In the nose, this change is best interpreted as a reactive phenomenon related to recurrent inflammatory episodes and irritation of the polyp's epithelium, and as such is just a further extension of the metaplasia of this epithelium. It is not possible from the available histological material to establish with any certainty whether it was the most dependent or low-lying part of the polyp which manifested this change.

Another possibility to be considered in the etiology of these nasal epithelial changes is viral infection.[13] Bizarre cytological changes can be readily induced in both tissue culture conditions[14] as well as in vivo[15] by such microorganisms as *Herpes simplex,* some of the adenoviruses, and the parainfluenza virus, all of which have an upper respiratory habitat. The papova group of viruses are also known to cause hyperplastic and papillomatous lesions in the nasal epithelium of humans,[16] and of horses.[17] Unfortunately, it was not possible to evaluate this viral hypothesis.

A condition which may possibly be confused with epithelial dysplasia or atypia, especially in a fragmented nasal biopsy, is the inverted papilloma of the nose or as formerly known, the Schneiderian or transitional cell papilloma.[9] The neoplastic epithelium which covers the surface and the sinus-like clefts of this tumor also has an abnormal epidermoid pattern and a distinct basement membrane. However, the component cells usually retain a uniformity and a polarity with reference to the basement membrane and the adjoining epithelial cells.[9] Their cytoplasm is rich in glycogen and only a very occasional mitotic figure can be observed. Intraepithelial cyst-like spaces and inflammatory cells usually are interspersed with the epithelial cells. These papillomas almost invariably arise from the nasal septal surface as opposed to polyps, and often recur.

The relationship of these changes to nasal epithelial and nasal sinus squamous carcinomas is difficult to evaluate. Changes similar to those described in these polyps can be seen in the mucosa adjacent to sites of frankly invasive cancer. On the other hand, the focal nature and the restricted extent of the changes described make such a possible relationship to infiltrating carcinoma less remote.

CONCLUSIONS

1. A small proportion (1.8%) of simple nasal mucous polyps showed a focal dysplastic change of their surface lining with no related changes in the immediately underlying stroma.

2. These patients did not form a recognizable group clinically.

3. On follow-up none of the patients showed a recurrence and in no case did invasive features supersede: these changes appear to constitute a local reaction to recurrent "irritation."

4. No radical surgical procedures appear to be indicated in these cases but clinical follow-up is essential.

5. Routine histopathological examination of all nasal polyps may help to further elucidate the causation of such epithelial changes.

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LYMPHOCYTE MORPHOLOGY IN MUCOID MIDDLE EAR EFFUSIONS

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SUMMARY—Cytologically, the mucoid middle ear effusions could be divided into a lymphocyte-monocyte type and a type where the granulocytes predominated. By α-naphthyl-acetate esterase (ANAE) staining procedure the T lymphocytes were found to make up the majority of lymphocytes in the first type, often accompanied by large numbers of ANAE-positive macrophages. In the second type the relative and particularly the absolute numbers of T cells were smaller. The T lymphocytes in aural effusions, distributed in agreement with their normal distribution in blood, could be the basis of possible delayed hypersensitivity immune mechanisms in the middle ear, but definite proof, either demonstrating receptor molecules directed to antigens or a specific response by T cells, is still lacking.

The cellular picture of aural secretions was discussed at some length even before the concept of secretory otitis media (glue ear) was established.[1,2] In acute purulent otitis media polymorphonuclear leukocytes predominate at first, but in a few days lymphocytes and macrophages of various sizes appear in the secretion. The macrophages increase in number in the course of the otitis being present, especially in reparative areas and absent from areas of active tissue destruction.

Senturia[3] classified the glue ear secretions into mucopurulent effusions, where large numbers of polymorphonuclear and mononuclear leukocytes are present, and mucoid effusions with much smaller numbers of cells, mainly of mononuclear type. Palva and Holopainen[4] found lymphocytes to be the dominating cells in glue ear effusion fluids together with polymorphonuclear leukocytes and macrophages. Eosinophilic cells are only rarely seen in glue ear secretions.[1-4]

In this investigation we have analyzed the cytology of glue ear secretion especially focusing attention on the presence of T lymphocytes in the infiltrates. On account of the very small cell yields, it was not possible to use "ordinary" laboratory methods, such as sheep erythrocyte (SRBC) rosetting,[5] to detect the T lymphocytes. We therefore used acid α-naphthyl acetate esterase (ANAE) as a marker for T lymphocyte.[3,6,7] The ANAE marker is present in approximately 85% of human T lymphocytes and absent from 90% of human B lymphocytes,[8] and histochemical staining for the demonstration of esterase activity may be performed directly on cytocentrifuged cell smears of aural secretions.

METHODS AND MATERIALS

The source material consists of 40 children hospitalized in the ENT Department for insertion of a grommet, in most cases combined with adenoidectomy. The blood chemistry studies included determinations of serum immunoglobulins, particularly IgE fraction, and counts of eosinophilic cells. Smears for nasal cytology and nasopharyngeal cultures for bacteriology were made. Part of the effusion fluid was submitted to the laboratory for bacterial culture, while the main part was reserved for cytological studies. All effusion samples studied belonged to the mucoid variety as judged by the naked eye.

To prepare cell smears for cytological examination, the aural secretion was diluted with phosphate-buffered saline and washed twice. The cells were centrifuged on to microscope slides with a cytocentrifuge.* After drying, the slides were stained with the May-Gruenwald-Giemsa stain for differential counting.

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Another set of slides was retained for esterase staining.

For demonstration of ANAE activity, the cytocentrifuged cell smears were incubated in a medium consisting of 40 ml of 0.067 M phosphate buffer, pH 5.0, 2.4 ml of hexazotized pararosaniline, and 10 mg of a α-naphthyl acetate* added to 0.4 ml of acetone. The mixture was brought to pH 5.8 using 1 N NaOH. Smears were incubated at room temperature for 3-10 h, washed in distilled water for ten minutes, dried and counterstained in 1% aqueous toluidine blue solution for 60 minutes. This counterstaining brought out the morphology of the preparations excellently and lymphocytes were easily distinguished from monocytes. A lymphocyte was scored ANAE positive when its cytoplasm contained a single spot or a few distinct spots of the reddish-brown reaction product.

For control we have tested the distribution of ANAE positive lymphocytes in the blood, in various lymphoid organs and in cell populations enriched or depleted of T lymphocytes. As reported elsewhere,[8] 76% of peripheral blood lymphocytes are ANAE positive and 56% of spleen lymphocytes and 55% of tonsil lymphocytes express the marker. While 84% of the SRBC rosette forming lymphocytes express the ANAE marker, at most 10% of surface immunoglobulin-carrying lymphocytes are ANAE positive. After SRBC rosetting-density centrifugation procedure, the T-depleted population (still containing 11% of SRBC-RFC) contains only 25% of ANAE positive lymphocytes, whereas the T-enriched population contains 86%. Approximately 40% of blood lymphocytes depleted both from SRBC-RFC and from surface immunoglobulin-carrying cells carry the ANAE marker. Thus it seems that the ANAE marker is predominantly confined to T lymphocytes and nearly entirely lacking from classical surface immunoglobulin positive B-cells and that, in addition to this, a fraction of null cells also express the marker.

RESULTS

Of the 62 samples obtained, 31 were sufficiently large to yield enough cells for differential counts, and in most cases also for ANAE staining. There were altogether eight ears in which monocytes, in particular, and lymphocytes were the dominating cells (Fig. 1), and the maximum relative number of granulocytes was less than 50%. In the remaining 23 ears the percentage of granulocytes ranged from 60 to 95, while the lymphocytes and monocytes constituted the minority (Fig. 2). There was a similar cellular response in seven bilateral cases. In two bilateral cases the one ear showed a lymphocyte-monocyte type of effusion and the other a granulocyte-type response; the disease had lasted for two years in both these patients, the secretions being sterile and thick in consistency. Otherwise the duration of disease ranged from three months up to two years but there was no clear relation between duration and cytological picture.

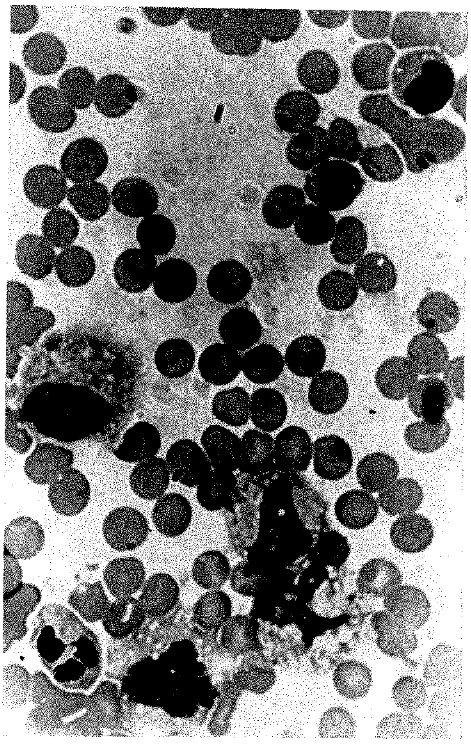

Fig. 1. Lymphocytic-monocytic type of effusion fluid. Among the erythrocytes, four macrophages, two lymphocytes and one polymorphonuclear leukocyte are seen. May-Gruenwald-Giemsa stain.

None of the children examined were found to have hypogammaglobulinemia. In one child the IgA fraction was definitely subnormal, but in all others the recorded values fell inside normal limits. The serum IgE levels were also within normal range for this age group, generally under 100 U/ml; the highest recorded value was 430 IU/ml. No patient showed a definite blood eosino-

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*Sigma Chemical Co., St. Louis, Mo.

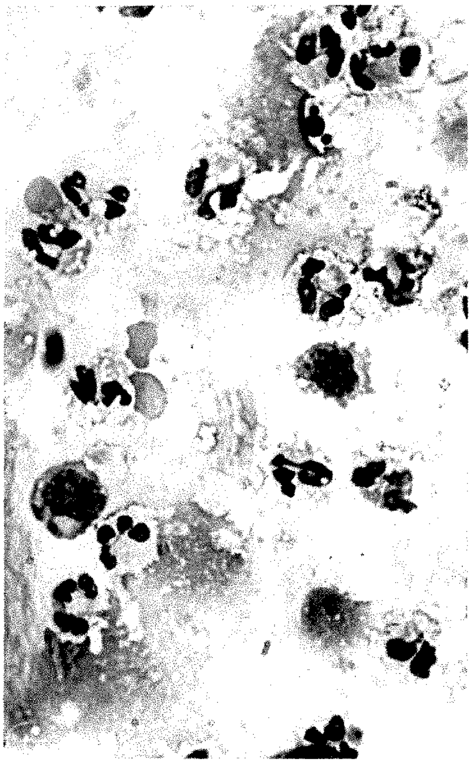

Fig. 2. Granulocytic type of effusion fluid. Among numerous polymorphonuclear leukocytes three macrophages are seen. May-Gruenwald-Giemsa stain.

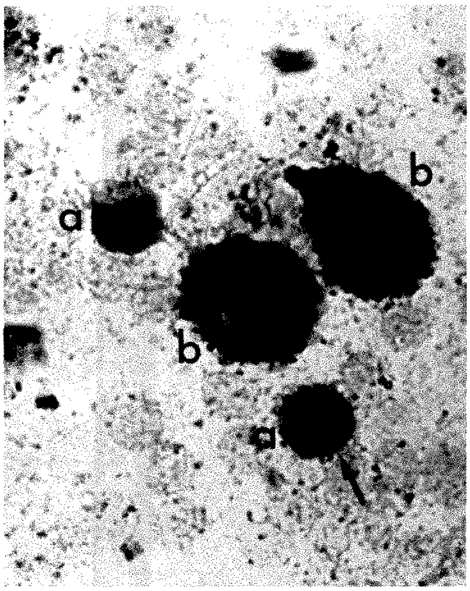

Fig. 3. Lymphocytic-monocytic type of effusion fluid. One lymphocyte (a) is ANAE-negative while another is positive, the arrow pointing to the ANAE-positive dot. Both macrophages (b) are strongly ANAE-positive. ANAE treatment counterstained with toluidine blue 0 stain.

philia. In half of the cases there were small numbers of eosinophils in the nasal smear but not enough to suggest an allergic response. During the early stages of disease *Hemophilus influenzae* and *Diplococus pneumoniae* were often cultured from the nasopharyngeal samples; in these cases the cellular picture of the nasal smear showed dominance of polymorphonuclear granulocytes.

At insertion of the grommet in 31 ears, bacterial culture of aural effusion proved sterile in 21 ears, in 5 ears there was a *Hemophilus influenzae* infection but pneumococci in none. *Staphylococcus aureus* and Neisseria were cultured twice, and *Staphylococcus epidermidis* once. There was no relationship between the result of the culture and the type of the aural effusion.

Seventy to 85% of the lymphocytes were ANAE positive in the eight lymphocyte-monocyte type of effusions (Fig. 3), excepting one in which 40% of lymphocytes displayed ANAE activity. In the granulocytic effusions the number of ANAE positive lymphocytes varied from 50 to 85% of all lymphocytes (12 ears), while in one ear the percentage was 43, in one 10 and in 4 only a few ANAE positive cells were found. Both in Figures 1 and 3 the effusions were predominantly monocytic. As most of the blood white cells are granulocytes, and as granulocytes form only a very small minority of the cell populations present in this type of infiltrates, any substantial contamination of the middle ear effusion by blood may be excluded.

As to macrophages and monocytes, three types of cells can be distinguished on the basis of ANAE staining:[9] macrophages with a diffuse staining throughout the cytoplasm, macrophages which are entirely ANAE negative, and monocytes with a single dot of ANAE activity. Macrophages of the first type were especially frequent in aural effusions of the monocyte-lymphocyte type (Fig. 3).

Evaluation of the patients granulocytic response in the cytotoxic food test of Bryan and Bryan[10] gave positive responses of a moderate or strong degree in nine children, most often to milk, wheat, orange and rye. Weak reactions to some food antigens were seen in all but two patients in whom the food test was totally negative. These two cases had the mucoid variety of effusion with high relative T-cell percentage. However, on the whole, the reactions did not correlate with the type of effusion, nor with the number of T-cells in the effusion.

DISCUSSION

In experimental studies on guinea pigs, Hussl and Lim[11] showed that by the action of ciliated, secretory and nonsecretory cells the middle ear mucosa is capable of absorbing various tracer substances, applied into the tympanic cavity. The particles were taken up by pinocytotic vesicles and transported through the mucosa, to be engulfed by tissue histiocytes or to be taken up into the lymphatics or blood capillaries. Retroauricular and junctional lymph nodes were positively identified as those draining the middle ear and Eustachian tube. It is possible that by this mechanism certain antigens would be recognized by the regional lymphocytes.

There is clear evidence that there is a strong response of immunocompetent cells in the middle ear submucosa in secretory otitis media, and that especially IgG, IgA and lysozymes greatly increase in the effusion as a result of local synthesis and secretory activity.[12-14] The absence of eosinophilic cells from the effusion is so conspicuous that regardless of occasionally raised IgE levels the immunopathologic Gell and Coombs type I reaction can hardly play any greater role in the etiology of this disease.

The present data as well as earlier communications[2-4] demonstrate that there are at least two cytological forms of otitis media with glue-type effusion. In the first type the cytological picture is dominated by lymphocytes and macrophages. The large number of ANAE positive lymphocytes in these secretions, approximately corresponding to the percentage distribution of T cells in blood, many indicate a delayed hypersensitivity reaction. In the second type, granulocytes strongly dominate and although the percentage values of T lymphocytes is comparable to those of the first type, their absolute distribution is much smaller.

It is obvious that the two cytological forms of secretory otitis media are in fact one disease, where the marked mononuclear cell response represents a more chronic phase often but not always preceded by the acute mucopurulent type.[1,2] On the basis of these findings it is not possible to conclude whether or not the T lymphocytes observed, particularly those in the lymphocytic-monocytic type of mucoid secretory otitis media, have any bearing on the putative delayed immune response taking place inside the middle ear. Before this question can be properly answered, either receptor molecules directed to the putative antigens or a specific response to these antigens by the infiltrating T cells must be domonstrated.

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HEAD AND NECK CANCER FELLOWSHIP

The American Society for Head and Neck Surgery is pleased to announce that it will sponsor a second fellowship in head and neck cancer at the M. D. Anderson Hospital beginning July 1, 1979. Applications are being accepted now and only until July 1, 1978. The fellowship carries an award of $5,000 in addition to the usual stipend for residents and fellows at the M. D. Anderson Hospital. For further information write: James R. Chandler, MD, Chairman, Fellowship Committee, American Society for Head and Neck Surgery, P. O. Box 520875, Miami, FL 33152.

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HUMAN TYMPANIC MEMBRANE – MALLEUS ATTACHMENT

PRELIMINARY STUDY

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SUMMARY — The relationship between the malleus handle and the tympanic membrane in humans has been studied with primary attention being directed to the fibrous layer of the tympanic membrane and its method of attachment to the malleus. This attachment is most intimate at the level of the umbo and becomes progressively more tenuous as the short process is approached. The long process of the malleus, comprised of a bony core, has a definite sleeve of cartilage surrounding its entire length. This cartilage is surrounded by a perichondrial layer which has previously been termed a periosteum. In the lower third, the fibrous lamina propria appears to split equally and the fibers then blend imperceptively with those of the perichondrial layer surrounding the manubrium. At high levels, the attachment is less intimate, most of the fibers appearing to pass lateral to the malleus handle. The embryologic development of the tympanic membrane-malleus junction has been considered and the anatomical features of this area have been considered in relation to functional requirements.

Further knowledge of the basic anatomy of the tympanic membrane and the ossicular articulations and attachments is important for the understanding of the basic vibratory pattern of the tympanic membrane. Several authors[1-8] have described the tympanic membrane fiber arrangements; only Longo[9] and Shimada and Lim[10] have discussed the tympanic membrane-malleus attachment. This preliminary report considers the relationship between the malleus handle and the tympanic membrane in humans, with primary attention directed to the fibrous layer of the tympanic membrane and its method of attachment to the malleus.

METHODS AND MATERIALS

For light microscopic study, ten human temporal bones without evidence of prior inflammatory disease were used. These bones had been decalcified in a 4.5% solution of ethylene diaminotetratracetic acid (EDTA) and then embedded in celloidin. Twenty micron-thick horizontal sections were cut and stained with H & E, and then mounted in Canada balsam.

RESULTS

A composite drawing of the tympanic membrane-malleus junction is shown in Figure 1. The manubrium will be considered at three distinctive levels: 1) at the umbo (A), 2) midmanubrium (B), and 3) in the upper third below the short process (C).

The relationship of the tympanic membrane and its attachment to the malleus handle varies greatly at each of these three representative levels. At the umbo (Fig. 2), the lateral squamous epithelial layer is apparent (A) with a loose subepidermal layer immediately beneath. The extremely thick lamina propria (B) is seen to divide equally as it approaches the manubrium and the fibers embrace this structure most intimately. The mucosal layer (C) is evident covering the fibrous tympanic membrane layer and then passing medial to the manubrium. At this level, the shape of the malleus handle is characteristically oval, the greatest diameter being in the anteroposterior direction. At a higher magnifi-

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From the Otologic Medical Group, Ear Research Institute, and the Department of Otolaryngology, University of Southern California, Los Angeles, and Project Hear, Palo Alto, California.

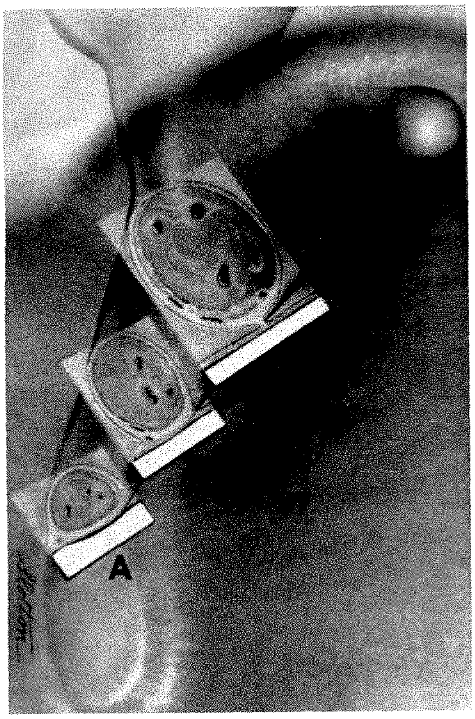

Fig. 1. Composite drawing, malleus handle and tympanic membrane junction. Note three layers of cross section, i.e., lower (A), mid (B), and upper long process of malleus (C).

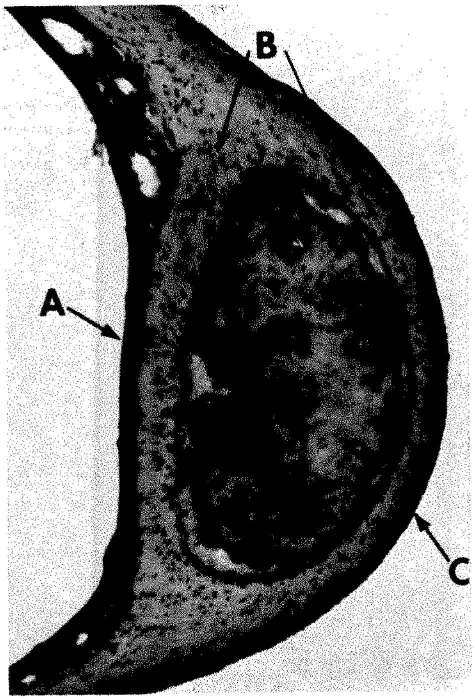

Fig. 2. Horizontal section, malleus handle at umbo level. The middle fibrous layer divides equally medial and lateral to the malleus handle. (A) Squamous epithelium, (B) fibrous layer, and (C) mucosa. (H & E, X 65)

cation (Fig. 3), the fibrous lamina propria is again seen to divide equally (A) and blend with the perichondrial layer overlying the cartilage (B) surrounding the bony core of the manubrium.

At the midlevel of the manubrium, the tympanic membrane-malleus relationships have changed greatly. The malleus handle has altered shape and is now elliptical in the mediolateral direction (Fig. 4). The cartilage (A) is now quite evident as it surrounds a bony core (B). The tympanic membrane now passes over the lateral surface of the manubrium. However, a significant portion of the lamina propria fibers pass medially to surround the malleus handle and blend with the perichondrial layer covering the cartilage (A). However, there appears to be a gradual reduction in the "bulk" of the fibers as they pass medially and this is clearly seen in Figure 5 at higher magnification. Here the fibrous layer is extremely thin (B) as is the perichondrium of the manubrium (C).

At the level of the upper third of the malleus handle (Fig. 6), the manubrium remains similar in shape to the lower level. However, the tympanic membrane, now itself noticeably thinner, passes at a distance lateral to the manubrium and appears attached by a mere "stalk" to the malleus handle. This attachment appears to have a fibrous core (B) and is covered by a mucosa (A) of the middle ear (Fig. 7). Over the lateral half of the manubrium, these fibers apparently arising from the lamina propria form a fairly distinct, thick layer blending with the perichondrium. However, more medially, as at lower levels, they become quite attenuated.

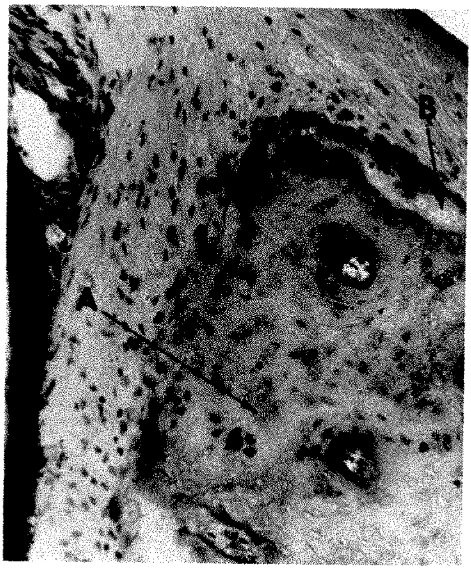

Fig. 3. Higher magnification of Figure 2. Note cartilage (B) covering bone (A) of malleus handle. (H & E, X 200)

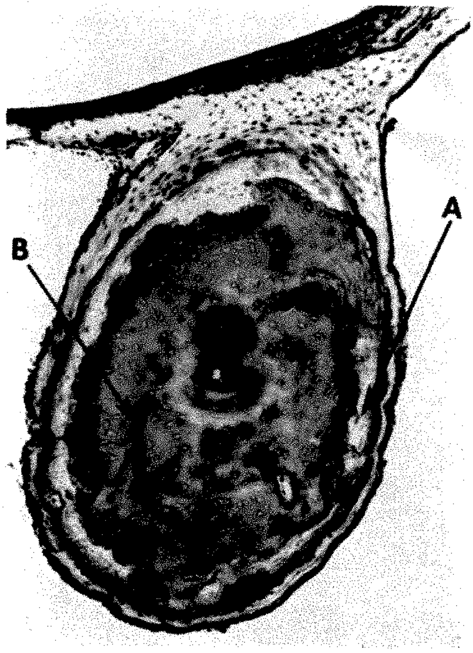

Fig. 4. Horizontal section, midmalleus handle. Note the change in shape of the malleus handle and the fiber investing layer around cartilage (A) and bone (B). (H & E, X 100)

DISCUSSION

A human tympanic membrane is formed from cellular connective tissue which later condenses to form the tunica propria of the tympanic membrane. This condensation occurs between the two cavities present at eight weeks of embryonic life and ultimately forms the tympanic cavity and the external auditory meatus. Within the cellular connective tissue is a mass of condensed mesenchyme which is the perimordium of the manubrium and handle of the malleus. The malleus forms from Meckel's cartilage (the first branchial arch) and is an entirely preformed entity. Not until the 111 mm stage of development does vacuolization occur in the cartilage which ultimately leads to ossification in this bone. In the adult, the long process measures 4.33 to 5.67 mm in length from the lateral process to the umbo. It is this longer length of the manubrium to which the tympanic membrane is attached. The entire length of the malleus regularly retains a layer of cartilage circumferentially surrounding the bony interior of the long process.[11]

Longo[9] categorizes the radial fibers taking origin from the handle of the malleus under three distinct groups: one, fibers arising from the upper third; two, fibers from the middle third; and three, fibers from the lower third of the handle of the malleus. In the superior one third of the handle of the malleus, the radial fibers from the anterior-superior quadrant also pass lateral to the handle of the malleus and terminate on the anterior aspect of the handle. He noted that both systems pass laterally to the handle of the malleus, while crossing each other to embrace the handle of the malleus. In the middle third of the handle of the malleus, the radial bundles from the anterior quadrant pass lateral to the handle of the malleus and insert on its anterior aspect. Once again, the malleus was felt to be embraced by collagenous fibers but in a manner slightly altered from the superior one third. The lower one third of the handle of the malleus in the region of the umbo was felt to give origin to radial fibers to both inferior quad-

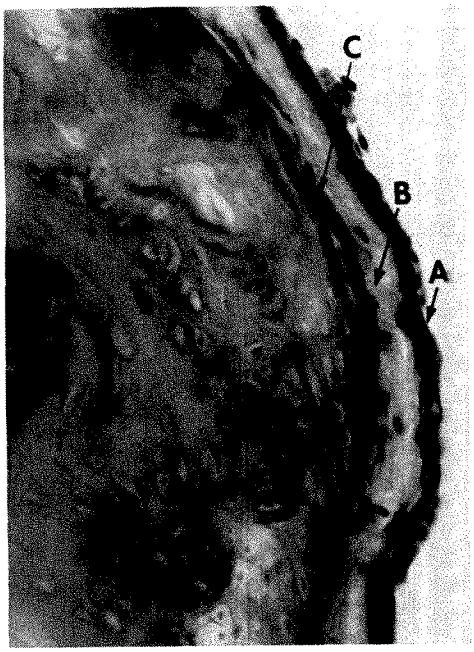

Fig. 5. Periphery, malleus handle. Note (A) mucosal, (B) fibrous, and (C) perichondrial layers. (H & E, X 400)

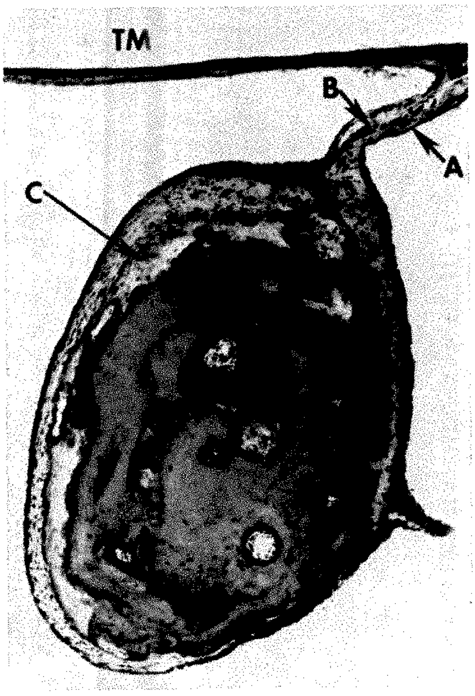

Fig. 6. Upper malleus. Note fine filament of mucosa (A), central fibrous layer (B) investing the malleus handle, and (C) cartilage surrounding bone of malleus handle. (H & E, X 100)

rants. Fibers which insert in the anterior-inferior quadrant arise from the medial aspect of the umbo, while fibers which insert in the posterior-inferior quadrant arise from the lateral aspect of the umbo. Shimada and Lim[10] felt that the radial fibers made firm contact with the lower four-fifths of the handle of the malleus and spread fanlike toward the annular ring of the tympanic membrane. The attachment of the radial fibers with the malleus varies from the short process to the umbo; in the lower one fifth of the handle of the malleus, most of the fibers attach to the bone from behind on the middle ear side. In the central three fifths of the handle of the malleus, the fibers attach to the periosteum of the handle of the malleus from both the canal and middle ear side. In the upper one-fifth of the handle of the malleus near the short process of the malleus, no trace of radial fibers could be found.

In the present preliminary study, we have been primarily concerned with the general relationship of the tympanic membrane to the malleus handle and the detailed description of the fibers of the attachment of the various components of the fibrous layer will form the substance of a subsequent report. However, from our studies, it does appear that in the lower one third (umbo) of the malleus handle there is equal bulk of fibrous layer both medial and lateral to the malleus handle. In the middle third, most of the substance of the tympanic membrane fibrous layer passes lateral to the malleus handle and the contact surface of the tympanic membrane and malleus handle is only approximately one sixth of the circumference of the malleus handle surface. While there do appear to be fibers passing medial to the long process, certainly the bulk of the tympanic membrane radial fiber layer passes lateral to the long process. In the upper one third of the malleus handle, only tenuous contact is made by the fibrous

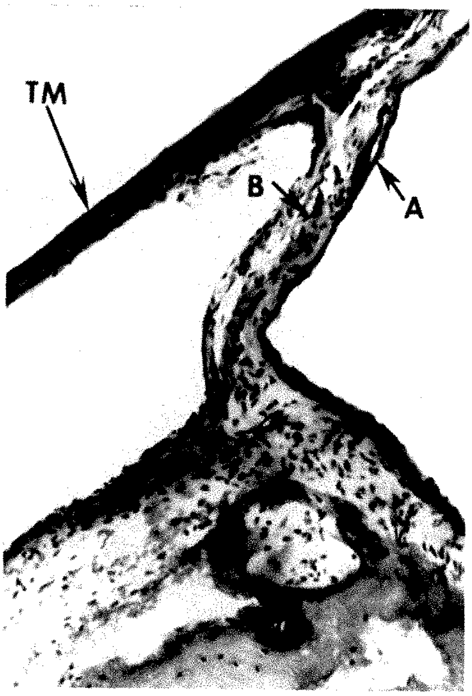

Fig. 7. Higher magnification of Figure 6. (H & E, X 200)

layer – a mere stalk attaching to the malleus handle.

The vibrations of the tympanic membrane-malleus complex have been studied by Helmholtz,[12] Dahmann,[13] Békésy,[14] and Wever and Lawrence.[15] More recently, Tonndorf and Khanna[16-18] and Khanna and Tonndorf[19] have described in great detail the vibratory pattern of the tympanic membrane, based on the application of time-averaged holography. They found that both the posterior and anterior portions of the tympanic membrane vibrate with larger amplitude than the manubrium mallei between them. This vibratory pattern agrees with the "curved-membrane" principle of Helmholtz[12] who had postulated that the tympanic membrane-malleus system should act as a transformer. Khanna and Tonndorf,[19] on the basis of their own data, calculated this transformer ratio and obtained an approximate value of two.

If the cone-shaped tympanic membrane were reinforced along one of its radii by a rigid strut of bone, the malleus handle, and if the connection between them were very tight, displacements of the kind described by Tonndorf and Khanna would let a considerable shearing stress develop between the membrane and the malleus, and this stress would impede their displacement. The type of connection described in the present paper could permit conversion of this stress into a sliding (shearing) displacement, so as not to impede it. Tonndorf and Khanna[16] have further postulated that for each strip of the tympanic membrane along the malleus the product of the curved-membrane layer and of the ossicular lever is constant (their Figure 8) so that in essence all of these "strips" contribute uniformly to mallear displacement. Thus, the action of the tympanic membrane is not concentrated at the umbo, as some of the previous authors had maintained. This part of their thesis is not altered by the present findings, since the tympanic membrane and the malleus are well coupled in the lateromedial direction by means of the extended stalk.

Thus, the tympanic membrane-malleus junction appears to be of vital importance in the transmission of sound from the tympanic membrane to the inner ear, and evidence to date suggests a very complex arrangement of individual radial fiber attachment to the malleus.

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Ann Otol 87:1978

Clinical and Surgical Notes

RECONSTRUCTION OF THE EXTERNAL EAR USING MULTIPLE BUROW'S TRIANGLES

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SUMMARY — Basal cell carcinoma of the auricle presents a challenge in both excision and reconstruction to the clinician. The following case report discusses and illustrates the use of controlled excision with assessment of margins and reconstruction using chondrocutaneous advancement flaps and multiple Burow's triangles.

The treatment goal with carcinoma of the external ear is to achieve the best functional and cosmetic result consistent with complete tumor resection. Many methods of excisional and reconstructive surgery are available to treat this disease. The following case presentation illustrates a simple technique that enables the physician to excise a lesion with an adequate tumor margin while confining his surgery to only one anatomic area.

CASE REPORT

A 73-year-old Caucasian male was initially seen in the Dermatology Clinic of Elmhurst General Hospital on April 11, 1977, with a .5 cm nodular lesion of the left helical rim which had been present for five months. The patient was subsequently seen in the Otolaryngology Clinic on April 21, 1977, at which time an incisional biopsy was done establishing the diagnosis of basal cell carcinoma of the left auricle. The patient was temporarily lost to follow-up and was not admitted for surgical excision of his lesion until June 14, 1977. During this seven week interval the lesion rapidly increased in size, measuring 1.5 cm in diameter on admission to the hospital (Fig. 1).

The patient was totally asymptomatic. There was no pain, bleeding, ulceration or induration of the surrounding skin. No lymph nodes were enlarged in the preauricular, postauricular or cervical areas. He had a history of chronic sun exposure during a lifetime of outdoor work. There was no previous history of skin carcinoma and the rest of his past medical history was unremarkable.

Due to the present size of the lesion. its rapid growth following biopsy, the possibility of cartilage involvement and the history of poor patient compliance, excisional surgery was thought to be a more appropriate form of therapy than radiation, topical chemotherapy or desiccation and curettage. The technique chosen involved excision and primary reconstruction of the helical rim using multiple Burow's triangles.

TECHNIQUE

The area of excision was infiltrated with 1% Xylocaine® with 1:100,000 epinephrine. Methylene blue was used to mark out two vertical lines on either side of the lesion and one horizontal line parallel to the helical rim, giving a tumor margin of 3 mm. A second line was drawn parallel to the previous markings in order to give a separate specimen for easy assessment of tumor margin and adequacy of resection (Fig. 2). The tumor was then excised full thickness including both skin and cartilage along the inner set of methylene blue lines. The second strip of tissue was

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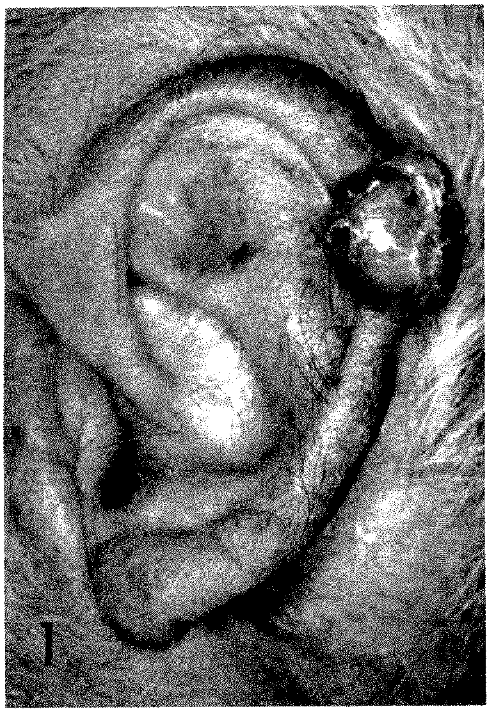
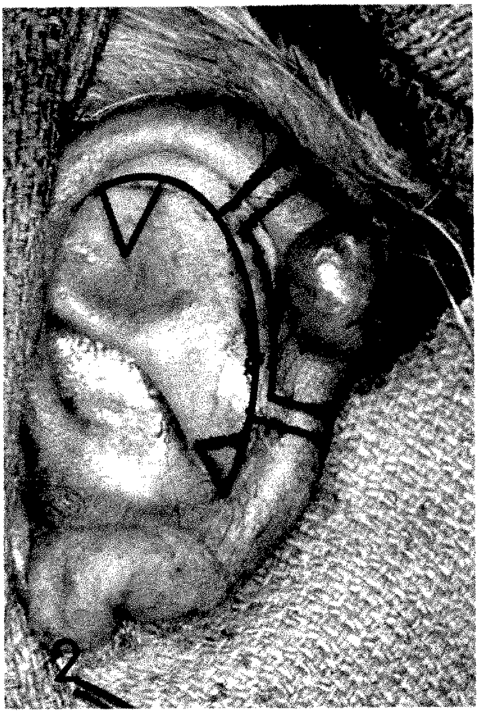
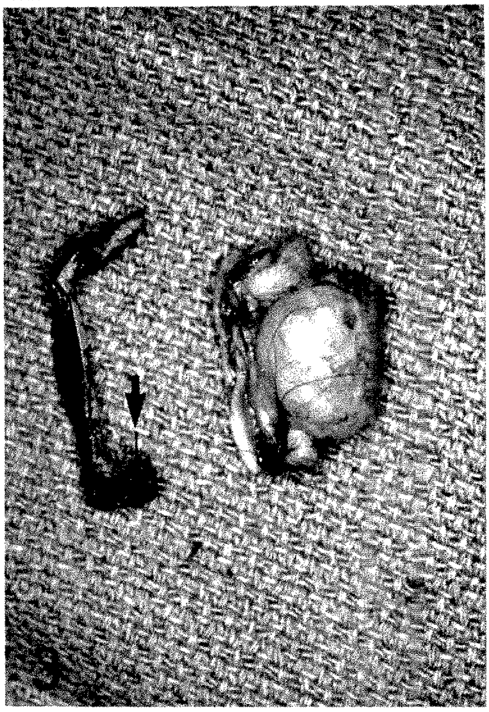






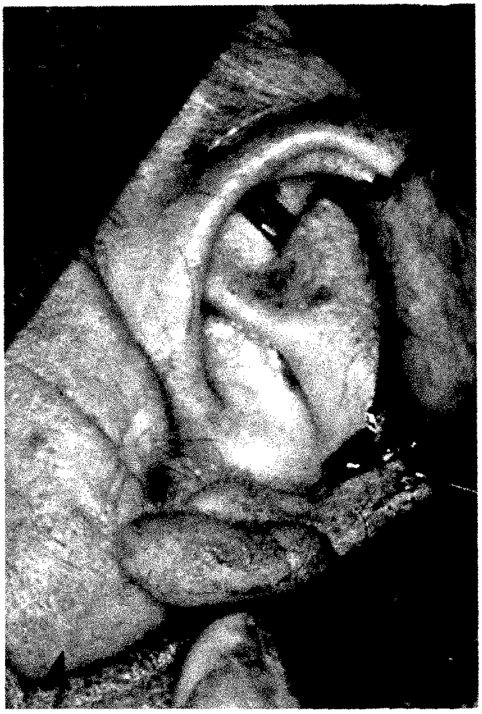
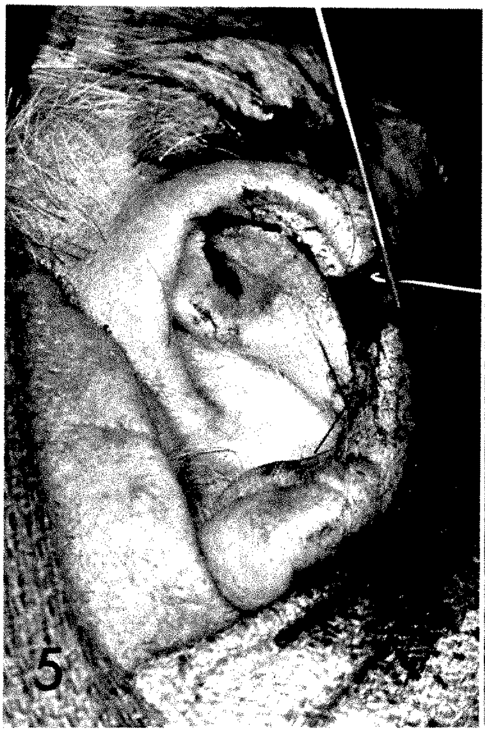


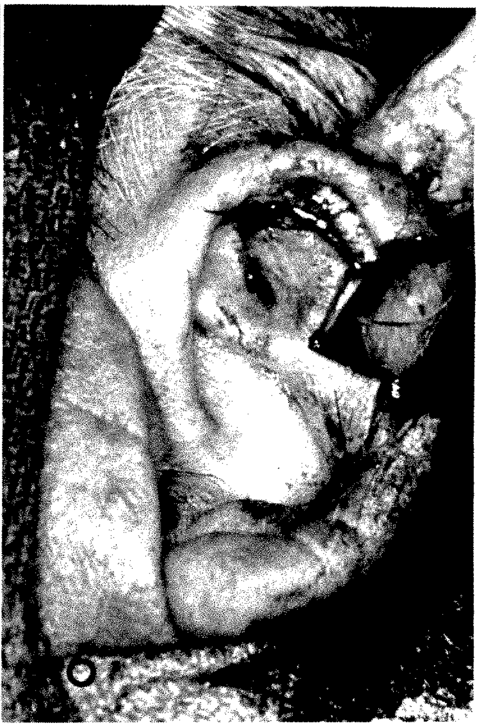
Fig. 1. Lateral view of left ear showing 1.5 cm basal cell carcinoma of helical rim.

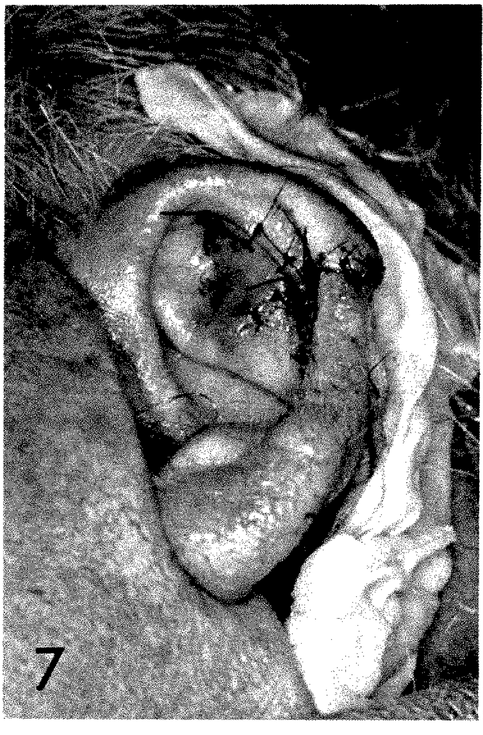
Fig. 2. Auricle marked with methylene blue indicating tumor specimen, separate margin specimen, and two Burow's triangles.

Fig. 3. Tumor specimen and separate margin specimen with lower border marked by suture (arrow).

Fig. 4. Appearance of auricle after excision of tumor and margin specimens, creation of chondrocutaneous advancement flaps and full-thickness resection of two Burow's triangles.







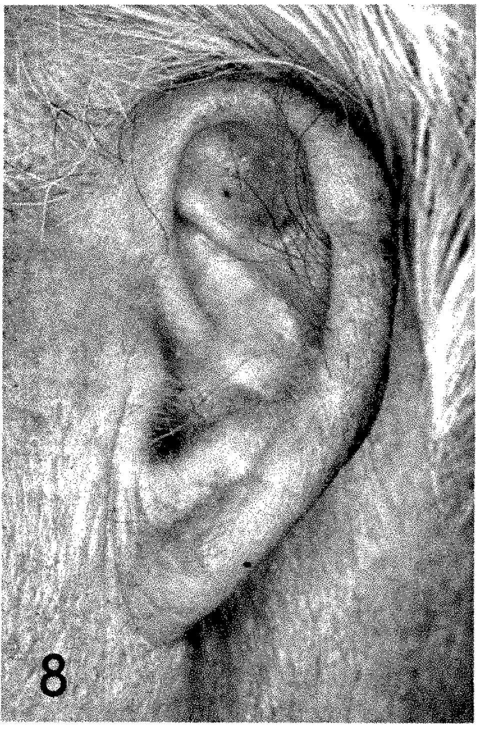


Fig. 5. Closure of Burow's triangles and attempted approximation of chondrocutaneous advancement flaps demonstrating persistent gap.

Fig. 6. Creation of third triangle to allow tension-free closure.

Fig. 7. Closure of all surgical wounds with interrupted 5-0 nylon sutures and post-auricular application of petrolatum-impregnated gauze.

Fig. 8. Appearance of reconstructed ear ten months after surgery.

then excised following the outer lines. A suture was placed on the inferior tip for orientation (Fig. 3).

After hemostasis was obtained with minimal cautery, the helical rims on either side of the excision were released from the scapha by incisions through the anterior skin and cartilage. In order to mobilize the helical rims into the defects a Burow's triangle was made at either end of the incisions (Fig. 4). Two triangles were not sufficient (Fig. 5) and a third triangle was made in the middle of the defect (Fig. 6). The addition of this triangle facilitated a tension-free closure of the defect (Fig. 7).

The skin on the posterior aspect of the Burow's triangles was not excised until the blood supply to the auricle was noted to be adequate. If the blood supply of the helix had been poor, the redundant skin would have been removed at a secondary procedure.

Interrupted sutures of chromic catgut were placed through the perichondrium and the cartilage to maintain the new position. The skin was approximated with interrupted 5-0 nylon sutures. Topical antibiotic was applied followed by a padded dressing. Sutures were removed on the fifth day. There was never any evidence of compromised blood supply.

FOLLOW-UP

The patient has been followed for one year with maintenance of a good cosmetic result and no evidence of recurrent disease. Sensation of the auricle is intact. The incisions are invisible except for minimal swelling of the superior or helical rim immediately above the closure (Fig. 8). The ear is approximately 5 mm shorter in vertical dimension than the opposite ear. However, this minimal disparity is only apparent when the patient is seen from behind and does not concern him.

DISCUSSION

Among the techniques which have been described for reconstruction of the external ear following trauma or surgery are postauricular skin flap,[1] chondrocutaneous advancement flap from helix[2] or postauricular region,[3] composite cartilage pedicle from anterior helix,[4] composite helical advancement flap,[5] free cartilage graft covered by auricular-postauricular flaps,[6] composed tubal pedicle[7] and composite graft from opposite ear.[8]

Among the factors to consider in selecting among these and other techniques are size of the defect, cause of the defect, condition and blood supply of tissues to be used in reconstruction, and motivation and cooperation of the patient. The last factor is particularly important when multiple staged procedures are contemplated. For most patients it is desirable to perform a one-stage procedure and to confine surgery to one area.

The case presented here illustrates a technique of controlled excision and primary reconstruction using chondrocutaneous advancement flaps and Burow's triangles. This technique is simple and gives a satisfactory cosmetic result while limiting surgery to one auricle.

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Ann Otol 87:1978

X-RAY OF THE MONTH

NEUROLEMMOMA OF MAXILLARY ANTRUM

ALFRED L. WEBER, MD
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PATIENT

A 16-year-old Caucasian female complained of nasal obstruction for eight years following an automobile accident. Because of increasing obstruction and intermittent pain in the left cheek and periorbital area, x-rays of the paranasal sinuses were obtained. There was no history of loss of vision, diplopia, facial paresthesia, dental pain or epistaxis. On physical examination a smooth mass was noted in the left upper nasal vault.

RADIOGRAPHS

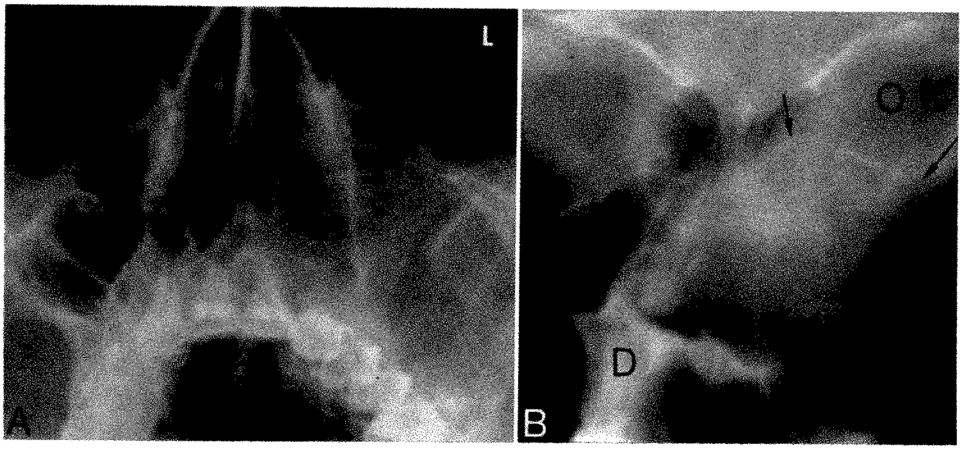
The Water's projection (A) reveals increased density and expansion of the left antrum. Polytome study AP (B) demonstrates displacement with thinning of the walls of the antrum (arrows). The soft tissue mass extended into the left nasal cavity. O - Orbit; D - Alveolar ridge.

DIAGNOSIS

A left Caldwell-Luc approach and a Denker extension through a left lateral rhinotomy were carried out. A soft yellow tumor filled the entire left maxillary sinus and extended into the left nasal cavity, ethmoid sinus and pterygomaxillary fossa. The histological diagnosis was neurolemmoma (schwannoma).[1,2]

DISCUSSION

At the Massachusetts Eye & Ear Infirmary and the Massachusetts General Hospital, 176 neuromas were found over a ten-year period, of which 148 were acoustic neuromas and 28 arose from other nerves.[3] These tumors arose in the jugular foramen, gasserian ganglion area, parasellar region, retrobulbar space, facial canal, parapharyngeal space, pterygomaxillary fossa, nasal



From the Department of Radiology, Massachusetts Eye and Ear Infirmary, and the Harvard Medical School, Boston, Massachusetts.

fossa, oral cavity, forehead and mandible. Symptoms may be related to the nerve involved or adjacent nerves being compressed by tumor. Because of their slow growth, these tumors characteristically expand and thin the bony confines of cavities or foramina in the facial and paranasal sinus regions. Laminography or computerized tomography are effective in demonstrating enlargement of these respective spaces. Angiography is often performed to differentiate schwannoma from vascular tumors such as chemodectoma or meningioma which may simulate them. Occasionally, schwannomas are very vascular. When they enlarge, they may outgrow their blood supply and undergo cystic degeneration in some areas. Malignant transformation rarely occurs. Computerized tomography may demonstrate the soft tissue component of the lesion in areas where no air interface is present, such as orbit, intracranial cavity, pterygomaxillary space and temporal fossa. This lesion should be differentiated from mucoceles, ossifying fibroma, ameloblastoma, dentigerous cyst, and other mesenchymal tumors.

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REFLECTIONS OF AN OTOLARYNGOLOGIST

THE DEVELOPING YOUNG MIND

WESLEY H. BRADLEY, MD
BETHESDA, MARYLAND

For many of us, I suspect, the pressures of everyday activities often prevent our noticing the interesting and enjoyable things which surround us. Unless we frequently remind ourselves to be aware and participate fully, we can "live" a number of days but miss out on many wonderful opportunities. A recent experience reminded me of this once again.

At the conclusion of a meeting in another city, one of the other guests and I were assigned to a member of the Otolaryngology house staff for the drive to the airport. The trip would require 45 minutes to an hour, and it was quickly evident that our driver was especially hopeful of spending much of the time talking with the other passenger. This was most appropriate as the young man serving as our driver had some questions regarding his research plans, and the other passenger was an authority in the area of the young man's research interest. With this established, I took the back seat, and helped direct the other passenger up front with our driver.

The two of them immediately put their heads together and for practical purposes were soon in a different world. At first I was a little concerned regarding the driving, for they were both completely intent on their discussion. However, it quickly became evident that a significant portion of the skills necessary for driving an auto operate at subcortical or even reflex levels. It was then I relaxed and, although I could have done some reading or other work, I made what I consider a much more sensible decision – I decided to listen to their discussion.

What a wonderful experience it was – truly a privilege. The younger man was well-prepared. His discussion of his thoughts and hypotheses showed that he had done much reading, thinking and working. His questions were logical and appropriate. The older man listened and answered some things, but then skillfully began to turn questions back to the questioner in a form designed to bring out new aspects not previously considered. To this the younger man responded; the discussion became more animated, and the beauty of the human mind and its capabilities was never more apparent. New thoughts, new ideas, new questions came forth, and we were at the airport before I could believe it. My plane was first, so they left me and still had further time to continue their discussion. I was almost a little envious at leaving.

What does this little episode signify, if anything? Certainly it would mean different things to different people. To the two individuals on the front seat involved in the discussion, I suspect it was simply a stimulating scientific interchange – exciting for the younger man and satisfying for the older man. As an observer, it created in me an awareness of that greatest of gifts – the human mind. To watch an inquisitive, well-disciplined mind function is a thrilling and yet in other ways a sobering experience. It made me even more aware of the responsibility each one of us assumes as a teacher, for we are then involved in the further development of a mind. The young people who come within our sphere of influence take from us not only what we offer and direct to them, but they also make observations and take away remembrances that perhaps we do not always intend for them to have. There is no greater responsibility than accepting the opportunity of helping to shape the development of a young person. It is this responsibility of which we must be continually aware.

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COMMUNICATIONS

Dear Editor:

Interest in the diagnosis and treatment of spastic dysphonia, the most mysterious of all disorders of the human voice, has revived more recently. In the hundred years since the disorder was first described by Traube[1] all forms of therapy, ranging from voice training, drug therapy, to hypnosis and psychotherapy have been tried, all of them with equally disappointing results. More recently, surgery has been advocated by Dedo[2] to treat severe cases of spastic dysphonia.

In spite of a wide range of phoniatric research no consensus has been reached about the presence of objectively demonstrable etiological factors.[3] To make it worse no objective criteria have been established for identification of the disease as the basis of a creditable analysis of the effectiveness of any kind of therapy. Advanced cases of spastic dysphonia, quite obvious to the experienced ear, are sometimes overlooked or misdiagnosed. On the other hand, the diagnosis of spastic dysphonia is often made where the patient suffers only from a high degree of vocal hyperfunction.

The laryngoscopic examination is of limited worth in diagnosing the disease since quite often no visible abnormality can be found. The descriptive terminology, always a problem in identifying voice disorders, is no more satisfying than the physical examination to define spastic dysphonia.

It seems apparent that our entire approach to spastic dysphonia is in need of revamping. The greater emphasis should be shifted from the treatment aspect to the establishment of better criteria for proper identification which is the basis of all research.

Before more radical forms of therapy are used on a larger scale, intensive research is needed to promote general agreement on the etiology and the identification of the disease. In addition, objective evaluation of the results of any form of therapy should be undertaken by cooperative efforts of a number of centers of laryngeal research, possibly under the sponsorship of the American Academy of Otolaryngology.

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ABSTRACTS FROM NATIONAL AND INTERNATIONAL JOURNALS

Acute Tonsillitis Due to Gram Negative Bacilli: A Report of Ten Cases

Takayama S: Otolaryngology (Tokyo) 48: 885-892, 1976

Ten cases of acute tonsillitis, which were considered to be caused by gram negative bacilli (GNB) such as *Pseudomonas aeruginosa* and/or Klebsiella were reported. Although gram positive cocci are considered as the major causative factor of acute tonsillitis and GNB are not, the latter may produce acute tonsillitis, such as in the conditions of so-called superimposed infections. One case had been subjected to long-term administration of massive doses of tumor chemotherapeutic agents and antibiotics. Two cases had used steroid hormones over a prolonged period. In the other seven cases, antibiotics were administered for an unusually long period which caused alteration of the tonsillar microflora.

Pseudomonas aeruginosa and Klebsiella are resistant to the antibiotics frequently used today, and thus acute tonsillitis due to these GNB may increase in the future. It is important that throat cultures and sensitivity tests should be routinely done prior to the selection of antibiotics, otherwise GNB infection must be suspected when the state of acute tonsillitis is not improved within three or four days after the initiation of antibiotic therapy.

M. IGARASHI

Esophageal Disruption from Blunt and Penetrating External Trauma

Spenler CW, Benfield JR: Arch Surg 111: 663-667, 1976

The authors report 11 cases of esophageal perforation secondary to external trauma over a nine-year period from a large county-referral hospital. One patient developed a cervical esophageal laceration secondary to a flexion-hyperextension injury of the neck with the tear adjacent to an osteoarthritic vertebral body spur. The other ten cases, five of whom had cervical esophageal lacerations, were due to penetrating wounds, most commonly gunshot wounds.

Early signs of esophageal injury, such as cervical or mediastinal air, were sometimes overlooked or ascribed to other conditions, such as a pneumothorax. If time and circumstances permit, the minimum evaluation for patients with suspected esophageal injury should include esophagoscopy, esophagogram with water-soluble contrast media, and bronchoscopy. If, due to other injuries, there is time for only one preoperative test, esophagoscopy should be chosen. The authors stress the importance of prompt recognition of esophageal injuries and recommend primary closure with drainage as their treatment of choice.

S. WETMORE

Humoral Immunity to Herpes Simplex Viral Induced Antigens in Smokers

Smith HG, Horowitz N, Silverman NA, et al: Cancer 38:1155-1162, 1976

Antibodies to herpes simplex viral-induced antigens (HSVIA) were assayed in 93 cigarette smokers, 75 of whom consumed alcoholic beverages, and in 94 nonsmoking, sex- and age-matched controls. Smokers demonstrated a six-fold increase of serum IgA antibodies to HSVIA over nonsmokers. These elevated titers were detected most frequently in smokers with ten or more pack-years of cigarette exposure. Similarly, IgA anti-HSVIA titers of smokers who consumed alcoholic beverages were found to be significantly higher than those of non-drinking smokers.

The frequency of IgG and IgM anti-HSVIA was comparable in smokers and nonsmokers, but anti-HSVIA titers were significantly higher in smokers. The increased frequency and titers of IgA anti-HSVIA occurred independently of IgG anti-HSVIA.

This study indicates that cigarette and alcohol use can change the pattern of humoral immunity to HSVIA.

J. NYSATHER

Effect of Intravenous Hyperalimentation on Established Delayed Hypersensitivity in the Cancer Patient

Copeland EM, MacFadyen BV, Dudrick SJ: Ann Surg 184:60-64, 1976

The authors report beneficial effects of nutritional repletion on immunocompetence and the response to oncologic therapy in 47 malnourished cancer patients. Patients were selected for the study because they were considered unsuitable for curative or major palliative therapy on nutritional grounds. All received intravenous hyperalimentation (IVH).

Prior to IVH, 33 patients (70%) had negative skin tests. Of this anergic group, 57.5% converted to positive and 42.5% remained negative during IVH. Of the 23 patients receiving chemotherapy, 17 had initially negative skin tests. Thirteen (76%) of these patients converted to positive with IVH. A response to chemotherapy occurred only in those patients whose skin tests were positive and surgical patients with positive skin tests did not suffer postoperative complications.

The authors conclude that the absence of delayed sensitivity in the cancer patient is probably due to malnutrition and can be restored by nutritional repletion.

J. KOUFMAN

Immunobiology of Operable Breast Cancer: An Assessment of Biologic Risk by Immunoparameters

Wanebo HJ, Rosen PP, Thaler T, et al: Ann Surg 184:258-267, 1976

Immunologic parameters of 134 patients with operable breast cancer and 63 patients with benign breast lesions were assessed in an attempt to determine whether immune function is related to risk of recurrence. The immunologic evaluation of these patients did not include an assessment of immunity specifically directed against tumor, but did include an extensive battery of tests which are designed to indicate the patients' degree of immune reaction.

DNCB sensitization, absolute lymphocyte levels, T-cells counts, and recall antigen skin tests were normal in those patients studied. Lymphocytic responses of cancer patients to *Candida albicans* and *E. Coli* were significantly depressed. Similarly, B cells bearing complement receptors were decreased in cancer patients, whereas B cells bearing surface immunoglobulin were increased.

Patients with a low risk of recurrence (noninfiltrating cancer without node involvement) had markedly lower lymphocytic responses to mitogens and antigens than patients with a greater risk of recurrence. A significant linear correlation between lymphocyte response to PHA and increasing pathologic stage or "risk of recurrence" was noted. The authors believe their study suggests that the PHA response is ". . . markedly influenced by the primary tumor burden and thus indirectly reflects the risk of recurrence."

This study further demonstrates the significance of immunologic evaluation in the complete assessment of cancer patients.

J. NYSATHER

Complications Following Surgery for Cancer of the Larynx and Hypopharynx

Gall AM, Sessions DG, Ogura JH: Cancer 39:624-[illegible]31, 1977

One thousand and thirty-five medical records of head and neck cancer patients were reviewed in this retrospective study to evaluate complications after surgery for cancer of the larynx and hypopharynx. All patients received their primary treatment at Washington University Medical Center from 1955 to 1972. Statistical analysis of the results showed cancer at the surgical margins to be significant in determining subsequent complications ($P < 0.001$). Age, sex, race, site and stage of primary tumor, and the presence of pretreatment cervical lymph node fixation did not alter the rate of complications. Low dose preoperative irradiation (3000-4500 rads), various forms of carotid artery protection (dermal graft, muscle flap), and surgical pathology findings including the size of the tumor, number of positive cervical nodes, and cellular characteristics of the tumor showed no significant effect on the rate of complications.

Common complications included wound infection and or necrosis, salivary fistula, hemorrhage, and carotid artery catastrophe. It is mentioned that duration of the surgical procedure "appears to be" related to the incidence of complications, but no data is presented. Results from other series are presented and the present data compares favorably with these other series.

D. LEOPOLD

Otitis Media and Cochlea: Morphological and Biochemical Studies in Guinea Pigs

Hache U, Gerhard HJ, Scheibe F, et al: Arch Otorhinolaryngol 214:49-61, 1976

The authors investigated the protein pattern and concentration in the perilymph, the serum, and the CSF in guinea pigs with unilateral otitis media. Histology of the middle ear, including the round window, was studied six hours to 21 days postinfection. As the inflammation intensity increased, the protein concentration and number of cells increased in the perilymph of the infected ear, while no changes could be demonstrated in the contralateral ear, in serum or in CSF. The authors concluded that the protein increase in the perilymph immediately after the infection probably was due to an increase in the blood vessel permeability in the inner ear. As the inflammation intensity increased, the round window membrane was changed histologically allowing leucocyte infiltration into the cochlea.

J. Thomsen

Spontaneous and Positional Nystagmus in Healthy Persons Demonstrated Only by Electronystagmography: Physiological Spontaneous Nystagmus or "Functional Scar"?

Mulch G, Lewizki W: Arch Otorhinolaryngol 215:135-145, 1977

The authors examined 102 healthy persons, aged 11-70, for spontaneous and positional nystagmus. When the ENG was registered with open eyes in darkness, 63 of the 102 test persons had a horizontal spontaneous or positional nystagmus. Under the Frenzel glasses however, there was a nystagmus in only two of these test persons. With open eyes in darkness, the frequency and intensity was the same in all age groups. The authors feel they have shown that a physiological horizontal vestibular nystagmus does exist, and they share Kornhuber's opinion that at the present time, the examination with the Frenzel glasses in a dark room, together with positional test, represents the best method for differentiating between physiological and pathological spontaneous nystagmus.

J. Thomsen

Carotid Body Tumor: Resection or Reflection

Javid H, Chawla SK, Dye WS, et al: Arch Surg 111:344-347, 1976

Carotid body tumors were treated in 24 consecutive patients over a 20-year period and evaluated as to presentation, evaluation, therapy and results of therapy. Thirteen patients had previous surgical attempts at diagnosis or cure of their tumors. Three patients had bilateral lesions. Two tumors had malignant changes; total excision was not possible in two patients; postoperative mortality was 4%. Intraluminal shunting in the last eight patients reduced blood flow and allowed uninterrupted cerebral perfusion during the resection of the tumor.

Preoperative carotid angiography was used to define the extent of each lesion. This knowledge is used by the head and neck surgeon to perform a definitive primary procedure, avoiding cranial nerve damage due to scarring of an operative field previously opened for biopsy or incomplete excision.

The authors encourage excision as soon as these tumors are diagnosed, rather than waiting until they become symptomatic. Statistics are presented to show lowered mortality and good therapeutic results with this approach.

W. McMillan

Antithyroid Antibodies in Alport's Syndrome

Miyoshi K, Suzuki M, Okno F, et al: Lancet 2:480-482, 1975

Two Japanese families with a positive family history of Alport's syndrome, a disease involving nephritis and deafness, were reviewed to determine the presence of antithyroid serum antibodies. These antibodies are found randomly in 3% of the Japanese population. However, all four patients examined with the syndrome were positive for antibody. Also, blood taken from two other apparently normal members of these two families was positive. Serum T_4 and T_3 taken from one patient with Alport's syndrome and his asymptomatic mother suggested hypothyroidism, and biopsy of the mother's thyroid tissue showed chronic thyroiditis.

Thus, Alport's syndrome appears to have features of thyroid, renal and otologic disease, possibly as a hereditary autoimmune abnormality.

B. M. Costello

Vascular Supply to the Organ of Corti in Man

Nomura Y: Arch Otorhinolaryngol 214:213-220, 1977

Terminal microcirculation differences between basal and middle turns of the cochlea may explain some differential high tone sensorineural hearing losses.

The capillary distribution in the basilar membrane and the osseous spiral lamina was studied in 40 human temporal bones. There was no difference in the vascular patterns in cochleas from people of various ages. The capillaries were made visible with a histochemical technique demonstrating alkaline phosphatase. More capillaries were shown to run close to the outer spiral vessel (*vas spirale*) in the middle turn than in the lower basal turn. The vascular network of the osseous spiral lamina is richer in the middle turn than in the basal turn. The length of a segment of outer spiral vessel between capillary branches is longer at basal turn level than at middle turn level, and the distance between outer spiral vessels and inner spiral vessels is greater in the basal than in the middle turns. This makes the basal turns more susceptible to ischemia, and may explain the preferential high frequency hearing loss.

B. Smith

BOOK REVIEWS

The Hypopharyngeal Diverticulum: Endoscopic Treatment and Manometry

By *Joseph J. M. van Overbeek.* Paperback, illustrated, referenced, 136 pp, 1977. Van Gorcum & Company, Ltd., Assen, The Netherlands. Price Dfl. 40.00

This small paperback volume deals in great detail with this uncommon lesion. The 11 brief chapters, citing 189 references, cover the anatomy of the pharyngoesophageal segment, the mechanism of deglutition, the etiology of the hypopharyngeal diverticulum, its incidence, its symptoms, its diagnosis and its association with carcinoma at that level; the last four chapters are concerned with treatment, especially in a series of 107 cases seen at the University Hospital at Groningen, The Netherlands, in the decade 1964-1974. The cases in this series were treated transendoscopically, and the book is meant, evidently, to publicize and promote this old but widely-ignored operation. The last chapter presents the results of esophageal manometry done in 13 of those cases.

The first chapter, dealing with general anatomic background, could use more figures to augment its concentrated text. The second chapter, on deglutition, is neither complete nor critical. The third chapter describes, rather uncritically, the theories of pathogenesis. The subsequent chapters dealing with the series of patients studied, are generally lucid and informative. The endoscopic treatment described consists in the incision of the septum between the diverticulum and the proximal esophagus through a special esophagoscope designed for that purpose. The method is presented clearly, and its history is reviewed from its first use by Mosher in 1917. The incidence of complications in previously-reported series, and in this one, is compared with that in other series treated by transcutaneous operations. The incidence of complications associated with the transendoscopic operation is lower. This could, of course, be attributable to patient selection, or other variables. In none of these series were treatments randomized. The final chapter, dealing with the results of manometric study in 13 of the 107 cases, has many problems. The methods are not described well and the data presentation is incomplete and confusing. One is unconvinced that "sufficient indications were obtained to reject the hypothesis that increased resting pressure or insufficient relaxation of the sphincter could lead to diverticulum formation."

The book can be recommended for its review of the history of this lesion and its operative treatment, and for its description of the particular operative method that it promotes.

James Christensen, MD

Approaches to Vocal Rehabilitation

By *Morton Cooper* and *Marcia Hartung Cooper* Hard cover, indexed, 407 pp, 1977. Charles C. Thomas, Springfield, IL. Price $21.75

This text provides a valuable clinical insight into several traditional vocal therapeutics by voice scientists and well-known voice clinicians. The book provides some important updating information on voice registers and the interactions of pitch and loudness, as well as some encouragement to utilize more quantitative acoustic and/or aerodynamic instrumentation to document severity and progress in therapy. Several chapters reiterate traditional clinical paradigms but nonetheless have value to the experienced clinician as they are statements from well-recognized and long experienced voice clinicians.

The highlights of the text include 1) important reconsiderations of the pitch range and the registers by H. Hollien as they may alter the voice clinician's approach to appraisal and remediation, 2) an insightful didactic clinical interaction (verbatim) between W. Perkins and a client with contact ulcers that lucidly restates the important rules of vocal hygiene and therapy commencement, 3) an important and succinct statement by J. Shanks on the complimentary value of the artificial larynx devices for laryngectomees regardless of speech training objectives, and finally, 4) a chapter prepared by a voice and singing teacher outlining his approach to vocal disabilities. These highlights may be further reviewed for their contributions in the following paragraphs:

Chapter 5, on the registers and ranges of the voice by H. Hollien, outlines a new model of the vocal registers. That is, the normal voice exhibits three major voice registers, according to Hollien, the *loft* or the highest pitch range which has slightly more than a one octave range, the *modal* or the midrange register having one and one-half octave range, and the *pulse* or the lowest register which has usually only one octave as its range. The loft and modal registers are the most functional voice ranges and combined are referred to as the phonational frequency range which varies between 27 and 34 semitones or approximately three octaves. Hollien, through the use of tables and graphs, teaches the reader the value of knowing the acoustic, perceptual and physiologic correlates of these registers in dealing with voice clients. Any phonational frequency range less than two octaves should be considered inadequate and disordered, according to Hollien. This chapter ranks the highest in new contributions to voice pathology.

Chapter 9, on behavioral management of vocal abuse by W. Perkins, presents a verbatim management program with an adult with chronic vocal abuse common to males. Perkins describes his initial therapy and evaluation session in this chapter; the transcription clearly outlines the organizing techniques of setting up a vocal rehabilitation program utilizing the patient history and vocal examination.

Chapter 7, on general techniques and specific procedures for certain voice problems by D. B. McCloskey, presents an approach to vocal remediation through the eyes of a singing instructor. He describes his approach to therapy as an interesting combination of relaxation, breathing, postural and phonational drills. A novel combination of breathing drills and postural exercizes to obtain optimal pitch and quality phonation is presented.

Chapter 15, on variations on a theme through interpersonal therapy with alaryngeal patients by J. Shanks, provides a long awaited updated report on the variety of pneumatic and electrolarynx devices and their role in vocal reeducation. He argues well that there should not be a dichotomy between the use of the artificial larynx and esophageal voice production. Shanks encourages clinicians to introduce an instrument early (postoperatively) to allow the client to communicate immediately regardless of his future use of the artificial device or esophageal speech production.

One must be moderately disappointed that the text did not deal thoroughly with spasmodic dysphonia considering its recent resurgence in interest and new remarkable surgical rehabilitation breakthrough. Furthermore, little mention or emphasis was given to the voice disorders that accompany the neuropathologies. Hospital clinicians will notice this void. The text is a valuable addition to the voice pathologist's library. It is, however, less a good text for the undergraduate or neophyte, because of the assumptions of therapeutic efficacy, and better a text for the experienced clinician or graduate student who has read other publications or had voice therapy experience with the techniques discussed in the text.

RICHARD M. MERSON, PhD

Facial Nerve Surgery

Edited by *Ugo Fisch*. Hard cover, illustrated, referenced, indexed by contributor, 586 pp, 1977. Aesculapius Publishing Co., Birmingham, AL 35205. Price $65.00

This book contains the formal papers and the edited panel discussions presented at the Third International Symposium on Facial Nerve Surgery held in Zurich, Switzerland, August 9-12, 1976. Many of these describe scientific and technical advances which have been made in the management of facial paralysis since the Second Symposium which was held six years previously. Participants in the symposium included biochemists, physiologists, pathologists, otolaryngologists, neurologists, neurosurgeons and plastic surgeons. Each of the presentations and the panel discussions which were organized to emphasize features of the areas discussed are well-illustrated and are followed by an excellent bibliography.

Preceding the definitive sections of the book are five short articles which summarize to a considerable extent the discussions which follow. Those of Conley and Jongkees are of particular interest because the former indicates that there is no single operation for facial rehabilitation while the latter states that the need for decompression of the facial nerve for Bell's palsy has been reduced by the introduction of steroids.

The material presented is divided into 15 sections, all but 5 of which are concerned with the management of facial paralysis. These five sections pertain to the anatomy, physiology and pathology of the facial nerve, electrical and other tests of facial nerve function as well as those intended to aid in the localization of the injury to the nerve, hemifacial spasm, and methods of classification and documentation of results obtained by surgical intervention. The papers in all but two of the sections are written by authors who have made major contributions in their fields. In general, these are excellent, although the description of the vascular supply of the facial nerve may be somewhat difficult to follow because of differences in terminology. Each of these sections have one or more panel discussions of the subject matter with which the section is concerned. These panel discussions, as far as this reviewer is concerned, give a better idea as to the complexity of the problem at hand than does any of the individual papers. The remaining two sections consist of panel discussions only.

The subjects discussed in this book, with the exception of those dealing with the classification and management of parotid tumors and the place of irradiation therapy in their management, are pertinent to the treatment of facial paralysis. These two chapters could have better been included in a symposium on tumors of the salivary glands. Probably the most important points brought out by the participants of the symposium are that the results of surgical intervention, when necessary, will be less than perfect in most instances; an excellent explanation by Sunderland of why this is true; the recognition that the treatment of facial paralysis may require consideration of multiple methods of amelioration over a period of years; and that newer methods of rehabilitation of the paralyzed face may offer hope for those patients with long-standing facial paralysis.

On first reviewing this book the reviewer felt that it would be an excellent source of information of the latest knowledge concerning the facial nerve only for those interested in facial palsy. However, after considerable digestion of the vast amount of information contained in it, it appears that it would be an excellent source of reference for what can be done to rehabilitate a patient who exhibits paralysis of the face, and consequently, should be in every medical library in order that those practitioners who have little or no experience with facial palsy can better understand the problem and be better able to refer a patient with paralysis of the face whom they might encounter in their practice.

Frank D. Lathrop, MD

Logan Turner's Diseases of the Nose, Throat and Ear, Eighth Edition

Edited by *J. F. Birrell.* Soft cover, color and black and white illustrations, indexed, 435 pp, 1977. Year Book Medical Publisher, Chicago, IL. Price $14.95

The original aim of this text was to provide a comprehensive survey of otolaryngology for medical students and general practitioners and the present editor is following that tradition. The contributors are all Edinburgh otolaryngologists.

The book achieves a practical approach to medical problems, discusses basic principles and gives the reasons for treatment. Some of the simpler procedures of treatment commonly carried out in an otolaryngologist's office are fully described, but the details of operations are omitted. However, the aims of surgical treatment are discussed.

The text is divided into four sections which include the nose and paranasal sinuses, the pharynx and nasopharynx, the larynx, bronchi and esophagus, and the ear. Common conditions seen by general practitioners are covered in detail, more uncommon conditions are just mentioned or omitted. Malignancies are given inadequate coverage and reconstructive and esthetic surgery is totally omitted. Other than these deficiencies, the text covers general otolaryngology very well. It has adequate illustrations and is written so it is easy to read.

This book does achieve its stated aim; it is a good basic text of otolaryngology for medical students and general practitioners. For this level of training it is a good text and would be useful to its intended audience.

Robert M. Bumsted, MD

Year Book of Otolaryngology

Edited by *Michael M. Paparella* and *M. Stuart Strong.* Hard cover, black and white illustrations, indexed, 388 pp, 1977. Year Book Medical Publishers, Chicago, IL. Price $25.00

The 1977 edition of the *Year Book of Otolaryngology* contains factual and comprehensive abstracts of over 300 articles relevant to otolaryngology in the scientific literature up to January 1977. The articles are chosen not only from the standard otolaryngologic literature but from journals in plastic surgery, general surgery, radiology, pediatrics, anesthesiology and internal medicine. Each abstract is followed by cogent and critical editorial comments with those in otology provided by Dr. Paparella and those in other areas by Dr. Strong. The editors also offer 48 "questions for clinicians" at the beginning of the book, hopefully to stimulate reader interest. Complete bibliographic reference is provided so that the reader may consult the original paper for comprehensive evaluation.

The selection of articles is generally well-balanced with all areas of clinical otolaryngology and some basic scientific research represented. Since it is quite possible that the editors were not able to include all significant articles which they studied, it might be helpful in future editions to provide a list of those articles. The illustrations, tables and charts are generally clear and helpful.

Several abstracts appear in the wrong section. For example, one group of papers on the facial nerve and otologic tumors are listed in the otosclerosis chapter. However, the subject index at the end of the book should allow such errors to be remedied. In addition, the editors provide an author index which facilitates article retrieval.

In summary, this year book, like its predecessors, is a useful and inexpensive addition to the library of the busy clinician and resident who may not have time to consult all of the journals surveyed. The editors are particularly to be complimented for looking beyond the more generally read otolaryngology journals in compiling their material.

Frank E. Lucente, MD

Hals-Nasen-Ohren-Heilkunde in Praxis und Klinik (Volume 2)

Edited by *J. Berendes, R. Link,* and *F. Zollner.* Hard cover, German text, black and white and color illustrations, indexed, bibliography, 390 pp, 1977. Georg Thieme Verlag, Stuttgart, Germany. Price DM 430

The reviewed volume deals with a wide range of pathology, diagnosis and management of the various diseases and conditions of the upper and lower respiratory tract. Twenty-three authors, most of them outstanding German otolaryngologists, as well as two anesthetists, plastic surgeons and lung specialists contributed to the contents of this very well planned manual. The first nine chapters are devoted to the rhinology and paranasal sinuses.

In this section there is an excellent presentation of plastic and reconstructive surgical procedures of the nose and surrounding structures. This presentation may be very helpful for otolaryngologists dealing with ablative cancer surgery in terms of closure of large facial defects. Different approaches of reconstructive rhinoplasty are very well illustrated and the most current methods are described.

Chapter 28, which deals with pediatric rhinology, is interesting, especially in terms of the presentation of the role of the septum in facial growth.

A very precise description of anatomy and physiology of the respiratory tract helps to understand all kinds of diagnosis and therapeutic procedures, like tracheotomy, tracheobronchoscopy, mediastinoscopy, etc. Attention is paid to proper handling of the foreign bodies in the trachea and in the bronchi.

Last chapters deal with the local and general anesthesia in otolaryngology. These chapters are of great value to both otolaryngologists and anesthetists with special emphasis to the very specific field in which surgery is performed.

The book is written concisely and to the point, and is very well illustrated.

J. Bardach, MD

Orbit Roentgenology

Edited by *Peter H. Arger*. Hard cover, black and white illustrations, indexed, 274 pp, 1977. John Wiley & Sons, Somerset, NJ. Price $48.00

This text represents one of a series in diagnostic and therapeutic radiology produced under the general editorial control of Dr. Luther W. Brady. Dr. Arger and 14 authorities on various aspects of orbital diseases describe normal orbital anatomy using plain film and tomographic techniques.

The changes produced by developmental abnormalities, fractures, acquired diseases and tumors are cataloged. Vascular anatomy and both arterial and venous abnormalities are extensively illustrated. Sections relating the diagnostic value of computerized tomography, isotope scans and ultrasound are also included.

While descriptive material about paranasal sinus disease and other periorbital afflictions of concern to the otolaryngologist are rather short, each entity has an extensive reference list to original descriptions of the entity being considered. The book therefore has excellent reference value.

External carotid arterial anatomy around and within the orbit is particularly well-described and beautifully illustrated. One particular point of interest to the otolaryngologist is a description of the variations in origin of the ophthalmic artery. The authors refer to a report in which the ophthalmic artery originated in 2.2% of 170 patients from the middle meningeal artery, an external carotid branch. The implication of internal maxillary ligation or external carotid ligation with ophthalmic artery obstruction is emphasized.

Computerized tomography of the orbits and surrounding structures is well-presented with clear-cut examples. The illustrations were obtained with the older 120 X 120 matrix so that even better definition of the lesions described could be expected with more recent equipment having a greater matrix.

The section on orbital ultrasonography is particularly interesting in that the author illustrates the use of A-scan ultrasound examination in differentiating between orbital cellulitis and abscess formation complicating paranasal sinus inflammatory disease. Venography in association with cavernous sinus obstruction is also well-illustrated.

Kenneth D. Dolan, MD

Microsurgery of the Temporal Bone and of Acoustic Neuromas

By *Albert L. Rhoton, Jr.* Soft cover, 1977. Paul C. Bucy & Associates, Tyron, NC. Price: $6.00

This monograph represents the experience and teaching of a neurosurgeon who has adapted microsurgical techniques to the removal of acoustic neuromas using the posterior fossa approach. Dr. Rhoton has presented a very useful and quite detailed dissertation of the anatomy, pathology and surgical technique important for the neurosurgical removal of tumors of the VIII nerve. The monograph contains three separate articles. The first article deals with the anatomy and osteology of the temporal bone in the form of a dissection manual. This manual is complete with regard to the instructions and instruments that are necessary for practicing surgical approaches to the internal auditory canal on the dry temporal bone. The translabyrinthine, posterior fossa and middle fossa approaches to the internal auditory canal are described in detail and with accuracy. The second article in the monograph deals with the neural and vascular relationships in the internal auditory canal which are important when dealing with tumors in this department. The effects of injury to the important structures in this region and suggestions as to how to avoid such complications are offered. In the final paper, the author describes in detail the surgical technique and instrumentation that is useful in the removal of acoustic neurinomas from the posterior fossa approach. I believe that for the price, this monograph is a very worthwhile addition to the library of the neuro-otologic surgeon.

Binaural Hearing Aids

By *Andreas Markides*. Hard cover, bibliography, indexed, 224 pp, 1977. Academic Press, London, England. Price $22.00

Markides presents the most comprehensive series of studies in the use of binaural hearing aids yet to appear as a unit in the literature. The bulk of this book, the format of which reminds one of a doctoral dissertation, describes procedures and results of experiments carried out by the author. The book begins with two chapters of literature review on binaural hearing and hearing aids. The review is quite thorough but only up through 1971. Chapter 3 describes the methods used in the investigations, Chapters 4 through 9 report the experiments and results, while Chapter 10 summarizes the main discussion and conclusions reached.

The experiments reported in this book represent a relatively thorough investigation of the binaural advantages in hearing speech and localization with a broad spectrum of subjects including people with normal hearing, with symmetrical and unsymmetrical conductive and sensorineural hearing losses, and unilateral hearing losses. The investigations covered monaural and binaural listening conditions with and without amplification.

Markides is to be complimented on his review of the literature and comprehensive investigations as well as his suggestions for the selection of candidates for binaural amplification. This is a book with which audiologists especially will want to become familiar. It offers the reader a succinct survey of the literature through 1971, a large body of research possessing a continuity of procedures and data treatment rare in the field of binaural hearing aids, and useful information for clinical decisions about the selection and use of binaural amplification.

CHARLES V. ANDERSON, PhD

Handbook of Sensory Physiology, Volume V/3 Auditory System: Clinical and Special Topics

Edited by *W. D. Keidel* and *W. D. Neff*. Hard cover, 343 black and white illustrations, referenced, indexed, 811 pp, 1976. Springer-Verlag, Berlin. Price $118.00.

This volume is part of a three volume set dealing with the auditory system which in turn is part of the complete 24 volume series. The publishers are to be congratulated on the high quality of paper, printing, and illustration. It is clear that this is a handbook meant to be used, rather than languishing on a shelf. Topics include: loudness and sensorineural deafness, bone conduction, electrical response audiometry, hearing and renal failure, community response to noise, cochlear mechanics, electrical stimulation in man and animals, pitch perception, infrasound, electrocochleography and drug ototoxicity.

The subject matter seems to be a peculiar combination of basic and applied topics including, for example, chapters as diverse as mathematical models of cochlear mechanics, community response to noise, and the effect of renal failure on hearing. If there is a central theme to the volume it is not evident. Consequently, there is something here for the taste of virtually any reader, but unfortunately in many cases it is only enough to whet the appetite. In addition, it appears as though the volume received relatively little attention from the editors in that 1) there is no foreword or introductory material of any kind (which might have placed the contents in broad perspective for the reader), 2) there is considerable repetition in the five chapters dealing with electrical responses to sound, and 3) slightly different systems for literature citation are followed by some chapter contributors.

One of the main strengths of this volume lies in its coverage of the use of electrical responses obtained from cortex, brain stem, and cochlea in the evaluation of hearing in man. Five of its 16 chapters, 40% of its pages, and 58% of its references are devoted to this topic. Another strength lies in the clarity of exposition of the authors. There are no bad chapters; some, however, are more easily read than others. A few of the chapters seem unnecessarily circumscribed. For example, I would have preferred to see the chapters on cochlear mechanics and models of the cochlea combined (they both dealt extensively with modeling.)

It is instructive to examine the distribution of references by year. For a handbook to be maximally useful it must provide substantial references for the subject matter it purports to cover. This volume does this admirably with over 2000 references. Hopefully references will reflect the most recent knowledge as well as the historical antecedents for each topic. The chapters are uneven in this respect. For example, several chapters show less than 5% of their references are drawn from the most recent five-year period. Other chapters showed a similar deficiency in early references. Clearly this may be a reflection of the chronology of the literature as well as the selectivity of the chapter authors. To the extent that it is the latter, it does not serve the best interest of the reader. On the whole, however, the references adequately sample our current knowledge in the topics selected for coverage.

This volume provides important and timely information in a variety of areas concerned with hearing. It will prove useful for students as well as active researchers.

ARNOLD SMALL, JR., PhD

Deafness, 3rd edition

By *John Ballantyne*. Paperback, black and white illustrations, indexed, 250 pp, 1977. Churchill Livingstone, New York. Price: $8.50

In 1960 John Ballantyne, FRCS, distinguished British otologist, wrote a unique personal monograph entitled "Deafness." He described it as follows: "This is deafness as seen and heard through the eyes and ears of one single otologist."

A useful book, it was written so clearly that it could be understood by the "intelligent layman — to the deaf and to parents of deaf children." The monograph, revised in 1970, has recently reappeared in a third edition (1977).

Mr. Ballantyne has well accomplished what he set out to do. The book deals, of course, in nontechnical phraseology with anatomy, acoustics, physiology, basic diagnostic approaches, and brief descriptions of the major causes of deafness. It contains useful and practical summaries of the various kinds of deafness, written especially for the nontechnical person, including the layman. It deals with such problems as ear infections, otosclerosis and comparable diseases, psychogenic lesions, rehabilitation, hearing aids, and contains a number of practical appendices dealing with education, rehabilitation and other facilities of special interest to British readers. It can be recommended as a very useful nontechnical well-written 250 page monograph for the person interested in an overview of the multifaceted aspects of deafness and the problems of deaf children and adults.

VICTOR GOODHILL, MD

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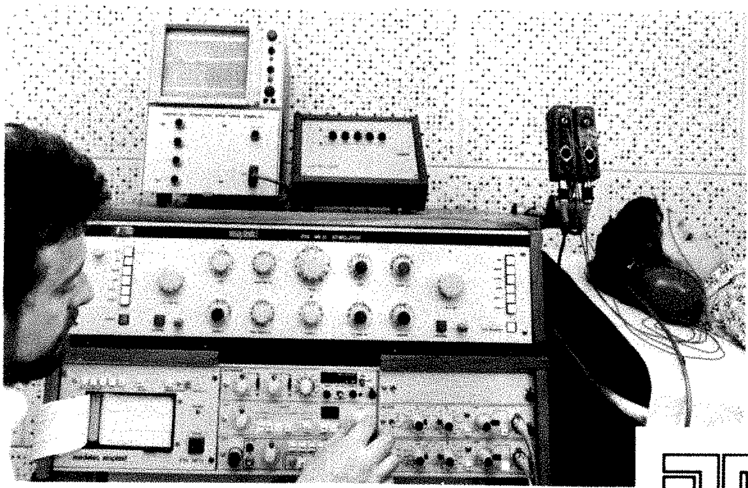

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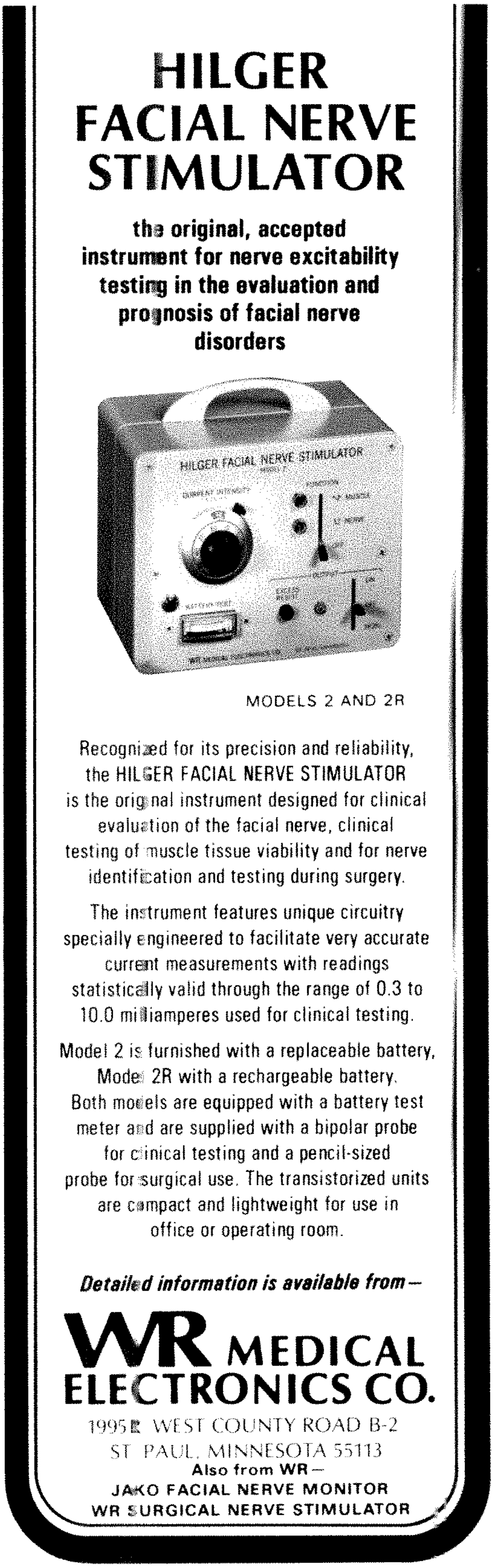

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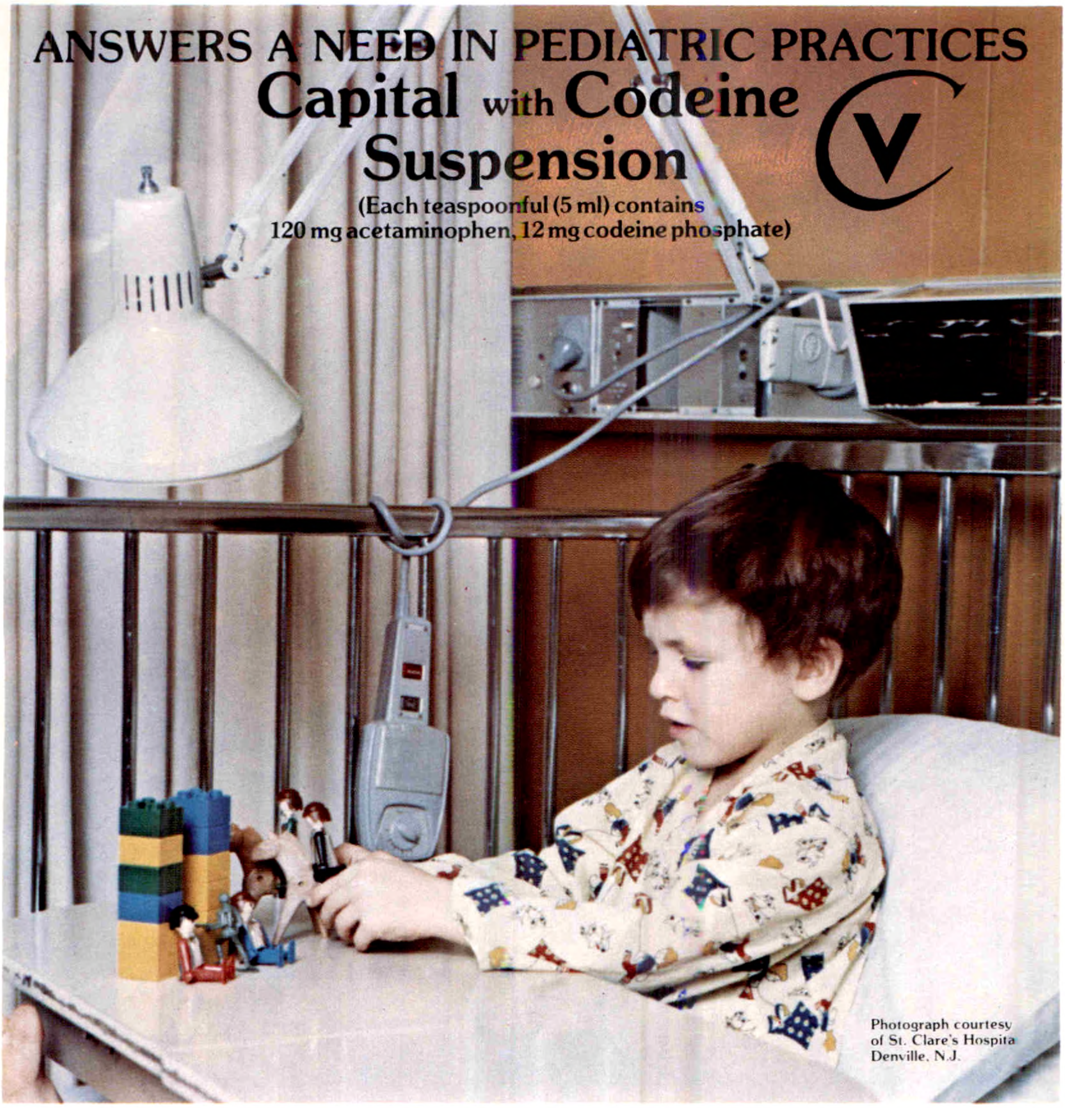

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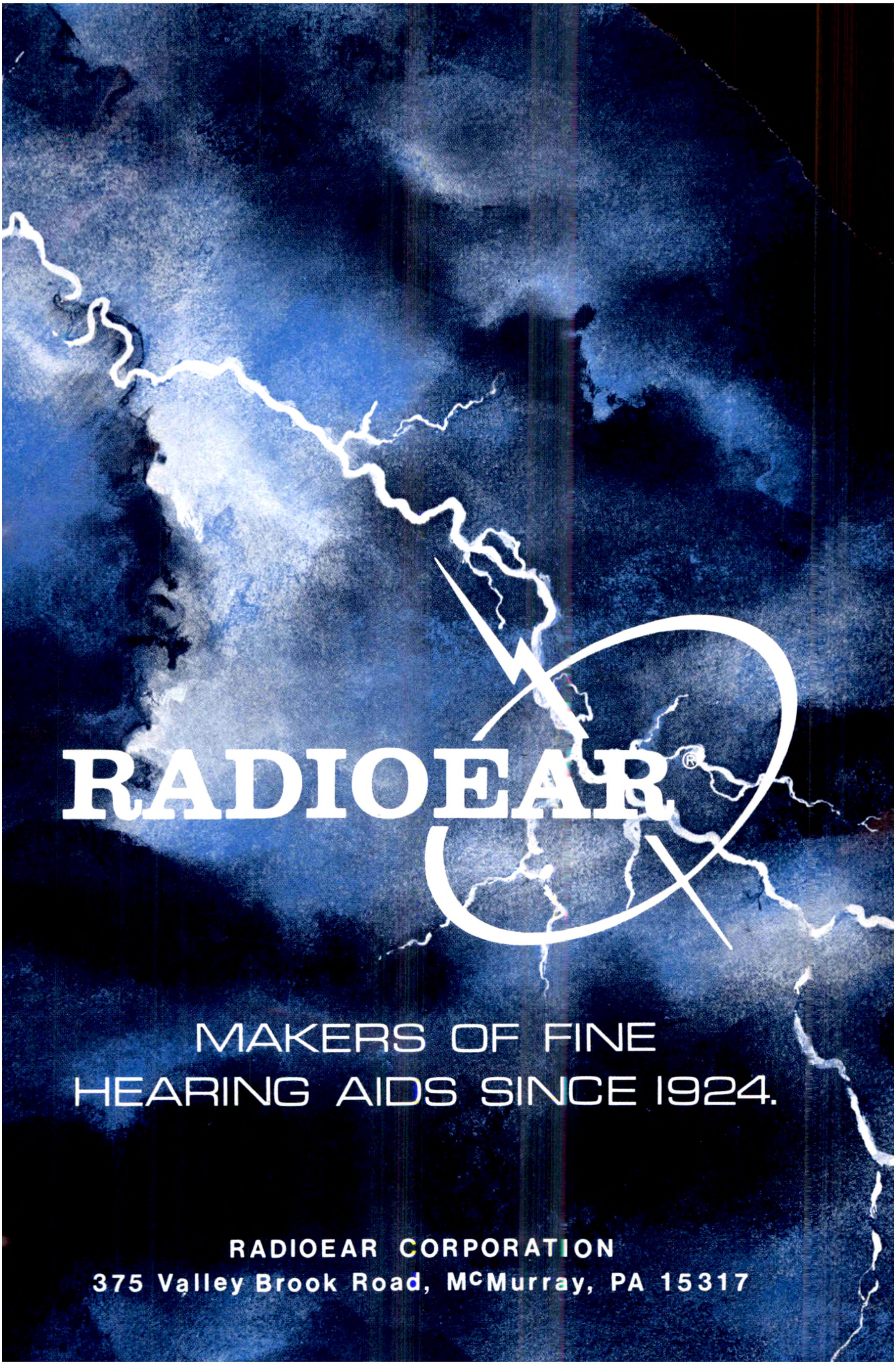
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SUMMARY — The postoperative findings in almost 800 stapedectomized ears were analyzed to evaluate the proposition that complication rates in stapedectomy were affected by the size of the footplate fenestration. It was concluded that small fenestra stapedectomy (diameter 0.4 mm) provided similar hearing gains to those achieved with standard techniques, that articulation problems occurred to a similar extent as with wire loop prostheses, and that there was a significantly lower incidence of a) fistula and b) immediate and delayed severe sensorineural hearing loss than with any other technique. There was also significantly less deterioration in bone conduction thresholds at 4 kHz after three years postoperatively. The incidence of severe immediate sensorineural loss in large fenestra stapedectomy (half or more of footplate removed) was significantly influenced by factors such as age, preoperative bone conduction thresholds and oval window pathology. A retrospective analysis provided no information which might predict oval window pathology. Additional information gained from the analysis indicated that with all types of stapedectomy, bone conduction did not deteriorate significantly more rapidly in the operated as compared to the unoperated ear, whereas in unoperated ears, deterioration in bone conduction was significantly greater in ears with mixed hearing losses than when the loss was purely sensorineural. It was concluded that small fenestra stapedectomy was currently the operation of choice because with it, the threat of cochlear dysfunction both immediately, and in the long term, was significantly less.

INTRODUCTION

Although most ear surgeons are now diagnosing otosclerosis less frequently and therefore it might be presumed that interest in stapedectomy would decline, there are potent reasons to support an alternative view.

First, some of the many patients already operated upon will eventually require advice about the management of a complication. Second, because hearing loss due to otosclerosis is so often bilateral, the search for a technique which will allow second ear stapedectomy with much more security than is possible at present, will continue.

The main problems which threaten the permanent success of all current methods of stapedial surgery include 1) the reoccurrence of conductive hearing loss due to a breakdown in the reconstructed ossicular chain, 2) immediate or delayed sensorineural hearing loss due to surgical trauma or fistula, and 3) progressive sensorineural hearing loss due to surgical trauma or cochlear otosclerosis.

Although Teflon® piston stapedectomy[1] and its various modifications may have advantages over other techniques, the main complications have not yet been entirely eliminated. However, thanks to a pursuit of Shea's basic philosophy to limit trauma to both incus and cochlea, a modification of the original Teflon® piston operation, small fenestra stapedectomy (SFS) using a much narrower piston (0.3 mm as compared to 0.8 mm diameter), has evolved* (Fig. 1).

This report is primarily concerned with evaluating the proposition that SFS effectively reduces the incidence of ossicular and cochlear problems

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*Cawthorne TE: Personal communication, 1965.

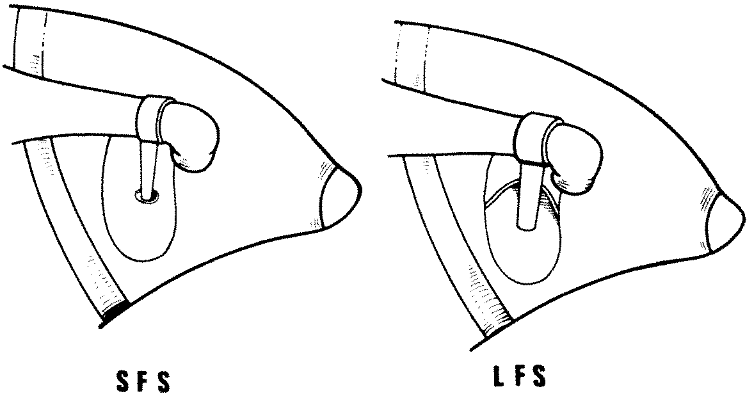

Fig. 1. Small fenestra (SFS) and large fenestra stapedectomy (LFS).

which detract from other methods of stapes surgery requiring the removal of much or all of the footplate, large fenestra stapedectomy (LFS). In addition, because our analysis has provided an opportunity to study the case histories of every patient in our series who has suffered complications and on the basis of the data we have accumulated concerning the possible causes of failure in several types of stapedectomy, we have attempted to formulate some policies about the management of postoperative problems.

The results of 715 stapedectomy operations carried out by two surgeons between 1960 and 1975 were analyzed. Eighty-seven percent attended regularly for follow-up at six months and then at one-year intervals. The remainder lapsed at some time postoperatively usually after several years. Only two patients were lost after six months. The analysis has four parts:

Part 1: Overall Functional Results. Information about age distribution, footplate pathology, closure of the air-bone gap and alterations in bone conduction thresholds and speech discrimination was documented to indicate the comparative success rates achieved with various techniques.

Part 2: Causes and Treatment of Mechanical Failure Following Stapedectomy. The records of all revision operations were scrutinized in detail in order to identify the cause of failure and evaluate our attempts to correct it.

Part 3: Incidence and Etiology of Severe Sensorineural Hearing Loss after Stapedectomy. The records of all patients who experienced immediate or subsequent sudden depression of bone conduction thresholds or speech discrimination scores by either 20 dB or 20% respectively, were examined in regard to factors which were considered as possibly contributory.

Part 4: Study of Cochlear Function in Small as Compared to Large Fenestra Stapedectomy. In order to evaluate the possibility that one fenestra size in stapedectomy might influence the rate of development of inner ear dysfunction more than another postoperatively, a separate study was carried out to measure changes in bone conduction thresholds in three subgroups of patients whose investigative data conformed to certain selected criteria in order to evaluate the roles played by the disease process, the overall effects of stapedectomy, and the fenestra size, in determining the future function of the cochlea.

PART 1: OVERALL FUNCTIONAL RESULTS

In order to establish the worth of small fenestra stapedectomy (SFS) as a technique, it was first necessary to discover whether SFS had provided improvements in air conduction through the speech frequencies and in speech discrimination comparable with large fenestra stapedectomy (LFS). In order to do so, the separate results obtained with the standard 0.8 mm diameter Teflon® piston, the 0.8 mm diameter Teflon® wire piston, the Gelfoam® wire prosthesis and the 0.3 mm diameter Teflon® piston were compared.

Because their investigative data failed to conform to prearranged criteria, the following categories of patients were excluded from this assessment:

1. Those who had no registrable preoperative bone conduction (operated upon with a view to improving their use of amplification).
2. Those in whom tests of speech discrimination were not carried out at all phases of their evaluation, usually early patients attending peripheral hospitals lacking this facility.
3. Those having any kind of prior ipsilateral stapes operation.
4. All those whose follow-up attendances were erratic. These were excluded to limit the problem of rogue sampling.[2]
5. All who suffered immediate severe depression of bone conduction (greater than 20 dB) postoperatively.

RESULTS

The analysis of the data on the 379 ears in this exclusive group was as follows:

General Profile.

1. Sex: 60% were female.
2. Average preoperative air conduction. In 76% this lay between 50 and 70 dB.
3. Average preoperative bone conduction. In 81% this was between 20 and 35 dB.
4. Preoperative speech discrimination scores: 56% varied between 92 and 80%.
5. The distribution of oval window pathology was: rim, 46%; biscuit, 34%; obliterative, 10%.
6. Prosthesis type: 0.8 mm Teflon® piston, 32%; 0.8 mm Teflon® wire piston, 24%; Gelfoam® wire prosthesis, 16%; 0.3 mm Teflon® piston, 27%.

Data Analysis. Changes in air and bone conduction thresholds (0.5 - 2 kHz) and speech discrimination scores at intervals of three and six months and 1, 2, 3, 4, 6, 8, 10 and 15 years postoperatively were documented on prepunched IBM cards which also recorded a number of other parameters which might influence the outcome. These included age in decades, the fenestra size, the footplate pathology, the prosthesis type and the preoperative bone conduction category.[3] This information was then analyzed by the ICL 1906S computer.

The method used was that recommended by the Otosclerosis Study Group. This uses the averaged preoperative bone conduction and postoperative air conduction (0.5 - 2 kHz) to compute the postoperative air-bone gap. "Success" was designated as closure of the air-bone gap to 10 dB or less. Changes in bone conduction thresholds of 10 dB or more in either direction were considered significant.

The significance of differences in the results were analyzed by Fisher's Exact Probability test. The results were looked at in two ways, the overall statistics obtained with the four prosthesis types by both surgeons, and the results obtained by each surgeon individually.

Air-Bone Gap. (Table 1). The postoperative air-bone gap at all follow-up periods for the four prosthesis types was compared. Using the criterion of success as a gap of 10 dB or less, and failure as a gap of 15 dB or greater, there was no significant difference in success rate between the prosthesis types at any follow-up period.

Perfect success (air-bone gap = 0) was also compared with any other result (air-bone gap = 5 or greater). For the follow-up periods between three months and two years, highly significant differences exist between the prosthesis types, the 0.3 mm Teflon® piston having a lower proportion of total success. On examination, however, most of these patients who were not a total success had air-bone gaps of 5 dB or 10 dB. For follow-up periods of three years and greater no significant differ-

TABLE 1. POSTOPERATIVE AIR-BONE GAP: COMPARISON OF SUCCESS/FAILURE RATIO BY TYPE OF PROSTHESIS

	*Observed Frequencies of Success and Failure**					
*Postop. Assessment Date** (yr)*	*0.8 mm Teflon® Piston*	*0.8 mm Teflon® Wire Piston*	*Gelfoam® Wire*	*0.3 mm Teflon® Piston*	*Total Patients*	*Probability†*
¼	171/15	135/5	89/6	153/10	584	NS
½	164/9	122/8	83/5	139/9	541	NS
1	157/12	117/8	79/6	109/5	493	NS
2	144/12	111/8	67/11	79/2	434	NS
3	123/12	102/5	59/7	28/1	337	NS
4	30/1	86/2	24/1	8/1	153	NS
6	32/1	84/3	32/2	8/1	163	NS
8	47/6	60/5	24/5	2/0	149	NS
10	26/2	25/3	8/1	1/0	66	NS

*Success defined as air-bone gap $<$ 10 dB; failure defined as air-bone gap $>$ 10 dB.

$\frac{171}{5}$ 171 - Numerator denotes number of successes in relevant category.
5 - Denominator denotes number of failures in relevant category.

**Follow-ups ¼ to 3 years tested by Chi-squared test; follow-ups 4 to 10 years tested by Fisher's Exact Probability test.

†NS denotes observed percentages not significantly different at 5% levels.

ence is observable in the proportions of total success. This may be because the numbers of patients decrease as follow-up increases, although it could have been expected that the numbers at three, four and five years would still have been large enough to detect any effect if it was present.

In summary, using conventional definitions of success and failure, the type of prosthesis was found to have no effect on air-bone gap closure. Using a very strict definition of success, the 0.3 mm Teflon® piston was found to have a lower number of perfect successes and a larger number of patients with gaps of 5 or 10 dB.

Alterations in Bone Conduction Thresholds (Table 2). The number of patients who suffered a loss of bone conduction 10 dB or more was significantly greater with the Gelfoam® wire prosthesis. When the results of the first surgeon were analyzed separately there were no significant differences between changes in bone conduction thresholds with any of the four prostheses. However, when the results of one surgeon were compared with those of the other, differences were observed. With the second surgeon, depressions in bone conduction thresholds with the Gelfoam® wire prosthesis and the 0.8 mm Teflon® piston were significantly greater than those occurring with the same prostheses when used by the first surgeon.

Speech Discrimination. A comparison between the results with each prosthesis was discarded when it was found that the results of speech discrimination tests had not been recorded routinely on many of the IBM cards used in this analysis. This problem did not arise with the analyses in Part 4 of this paper, when the data were taken directly from the hospital notes, put on work sheets and then transferred to the computer.

DISCUSSION

Overall, equally good results were obtained with each prosthesis in regard to improvement in air conduction thresholds, and these results are comparable to those reported elsewhere. In contrast, the results for bone conduction change are anything but straightforward. Of the nine follow-up periods tested, significant differences in success rates were observed for three of them.

The significant differences observed at three months, six months and two years are primarily attributable to the relatively low success rate observed in

TABLE 2. POSTOPERATIVE BONE CONDUCTION CHANGE: COMPARISON OF SUCCESS/FAILURE RATIO OBSERVED BY TYPE OF PROSTHESIS

	*Observed Frequencies of Success and Failure**					
Postop. Assessment Date (yr)	*0.8 mm Teflon® Piston*	*0.8 mm Teflon® Wire Piston*	*Gelfoam® Wire*	*0.3 mm Teflon Piston*	*Total Patients*	*Probability***
¼	181/5	136/0	89/6	162/0	597	<0.01
½	171/5	125/1	81/6	147/0	536	<0.01
1	167/2	120/2	82/2	112/0	487	NS
2	153/3	113/2	71/6	81/0	429	<0.025
3	130/5	98/2	60/5	28/1	330	NS
4	30/2	82/6	21/3	8/1	153	NS
6	32/1	85/2	30/2	9/0	161	NS
8	50/3	62/3	26/3	2/2	149	NS
10	28/0	26/1	7/2	1/0	65	NS

*Success defined as bone conduction change of <10 dB; failure defined as bone conduction change of >10 dB.

181 - Numerator denotes number of successes in relevant category.

5 - Denominator denotes number of failures in relevant category.

**NS denotes observed percentages not significantly different at 5% levels. (All probabilities calculated from Fisher's Exact Probability Test.)

the Gelfoam® wire prosthesis group. It is unclear from the results obtained whether the absence of significant differences for follow-up periods of three years and over is due to the long-term disappearance of any Gelfoam® wire prosthesis effect or rather merely a reflection of the decreasing statistical sensitivity caused by the falloff in sample size. In view of the fact that the percentage success rate for Gelfoam® wire prosthesis is consistently lower than for the other prosthesis types at all nine follow-up periods, the second explanation seems the more likely. We conclude therefore that these results indicate that a Gelfoam® wire prosthesis is associated with a less favorable bone conduction change than the other prosthesis types.

It may be that because these were all large fenestra operations they were essentially more traumatic due to prolonged instrumentation and incurred a risk of damaging hydraulic effects on the inner ear. The fact that these prostheses caused very little depression of bone conduction in the hands of the first surgeon as compared to the second, suggests the possibility that differences in surgical skill were responsible. Against this suggestion, an identical incidence of severely deafened ears in the series overall for both surgeons must be taken into consideration (see Part 3 of this report).

The possibility that differences in surgical skill affected the outcome is also suggested by the fact that LFS with the Teflon® wire prosthesis (0.8 mm) gave a very low incidence of bone conduction loss when used by the first surgeon. However, an alternative and better explanation may be that the insertion of the Teflon® wire piston into the oval window coupled with simultaneous articulation with the incus is a very much easier maneuver than the positioning of the standard 0.8 mm all-Teflon® piston. With the all-Teflon® prosthesis the time available for articulation with the incus after opening the loop is such that frequently several attempts at insertion were necessary. On the other hand, with the Teflon® wire prosthesis, the distal end of the prosthesis was inserted into the oval window and the wire loop manipulated at the surgeon's convenience over the incus. Usually only one attempt was necessary to make this articulation, and

TABLE 3. NUMERICAL RESULTS IN TERMS OF SUCCESS OR FAILURE OF AIR-BONE GAP CLOSURE FOR FOUR PROSTHESES AT 0.5 kHz

	0.8 mm Teflon® Piston	*0.8 mm Teflon® Wire Piston*	*Gelfoam® Wire Prosthesis*	*0.3 mm Teflon® Piston*
Perfect success*	28	81	22	53
Not perfect	25	63	6	141
		$X^2 = 45.95$ ($P < 0.001$)		
Acceptable success**	43	124	25	132
Failure	10	20	3	62
		$X^2 = 18.60$ ($P < 0.001$)		

*Air-bone gap = 0 dB or overclosure.

**Air-bone gap = 10 dB or less.

consequently there would be much less likelihood of trauma to the inner ear.

Because an earlier report had shown less effective closure of the air-bone gap for lower frequencies with a 0.6 mm piston,[4] the patients operated upon by the first surgeon were studied in greater detail in order to determine whether piston diameter had a significant influence on frequency success rates. Preoperative bone conduction and postoperative air conduction thresholds between 0.5 and 4 kHz were documented to compute the air-bone gap at 0.5, 1, 2 and 4 kHz, one year postoperatively for each prosthesis type.

Tables 3 to 6 contain the numerical results (in terms of success or failure of air-bone gap closure) for the four prostheses at each of the four response frequencies.

Two measures of success were employed. A perfect success was defined as a closure of the air-bone gap to 0 dB or overclosure. An acceptable success was defined as one in which the air-bone gap was 10 dB or less. Results are presented for both criteria.

The Chi-squared test was employed to compare the proportions of success and failure exhibited by the four prostheses groups at each given response frequency.

At 0.5 and 1 kHz both measures of success show very highly significant ($P < 0.001$) differences between the prostheses. These differences are attributable to the 0.3 mm Teflon® piston group exhibiting a very markedly higher proportion of failures than any of the other three prostheses.

At 2 kHz the complete success criterion shows highly significant differences ($P < 0.01$) between prostheses. The acceptable success criterion, however, shows no significant difference. The differences in complete success rates are again attributable to the fact that the 0.3 mm Teflon® piston group has a substantially higher failure rate than the other three prostheses.

TABLE 4. NUMERICAL RESULTS IN TERMS OF SUCCESS OR FAILURE OF AIR-BONE GAP CLOSURE FOR FOUR PROSTHESES AT 1 kHz

	0.8 mm Teflon® Piston	*0.8 mm Teflon® Wire Piston*	*Gelfoam® Wire Prosthesis*	*0.3 mm Teflon® Piston*
Perfect success	31	89	22	77
Not perfect	22	55	6	117
		$X^2 = 26.14$ ($P < 0.001$)		
Acceptable success	49	131	25	150
Failure	4	13	3	44
		$X^2 = 15.46$ ($P < 0.01$)		

TABLE 5. NUMERICAL RESULTS IN TERMS OF SUCCESS OR FAILURE OF AIR-BONE CLOSURE FOR FOUR PROSTHESES AT 2 kHz

	0.8 mm Teflon® Piston	*0.8 mm Teflon® Wire Piston*	*Gelfoam® Wire Prosthesis*	*0.3 mm Teflon® Piston*
Perfect success	43	121	21	130
Not perfect	10	23	7	64
		$X^2 = 13.99$ ($P < 0.01$)		
Acceptable success	51	138	26	179
Failure	2	6	2	15
		$X^2 = 2.43$ (N.S.)		

At 4 kHz neither criterion of success shows any significant difference.

It is clear, therefore, that prosthesis type has a marked effect on air-bone gap closure, the 0.3 mm Teflon® piston yielding markedly poorer results than any of the other three types (which show no significant difference from one another).

It is equally clear, too, that this phenomena is highly frequency dependent, being most dramatic at the lower end of the frequency spectrum, decreasing in magnitude as response frequency increases and eventually effectively disappears completely at 4 kHz.

CONCLUSION

In this series, although the performance of the SFS with the 0.3 mm Teflon® piston has been shown to be as good in terms of overall hearing improvement as that obtained with LFS, using any of the other prostheses, the low tone response is significantly less good. Our analysis shows that the safety factor for the cochlea was significantly better overall with SFS, but it is not clear from the information available whether this is due to a difference in surgical skill or to a difference in the amount of trauma inflicted upon the inner ear related to the fenestra size.

PART 2: CAUSES AND TREATMENT OF MECHANICAL FAILURE FOLLOWING STAPEDECTOMY

A survey of over 40 articles written in the last decade concerning the complications of stapedectomy indicates that although there are some differences over the relative importance attributed to certain problems, there is general agreement about the direction in which our research should now be directed. The situation is well summarized by Shea[5] who, in his 20-year report on fenestration of the oval window, made the observation that although the original objections to stapedectomy have all but disappeared, it was now increasingly necessary to concentrate on the problems arising out of the operation itself the chief of these being the reappearance of a conductive hearing loss after a successful initial result, and the

TABLE 6. NUMERICAL RESULTS IN TERMS OF SUCCESS OR FAILURE OF AIR-BONE GAP CLOSURE FOR FOUR PROSTHESES AT 4 kHz

	0.8 mm Teflon® Piston	*0.8 mm Teflon® Wire Piston*	*Gelfoam® Wire Prosthesis*	*0.3 mm Teflon® Piston*
Perfect success	27	57	7	70
Not perfect	26	78	21	124
		$X^2 = 6.74$ (N.S.)		
Acceptable success	44	96	20	150
Failure	9	38	8	44
		$X^2 = 3.53$ (N.S.)		

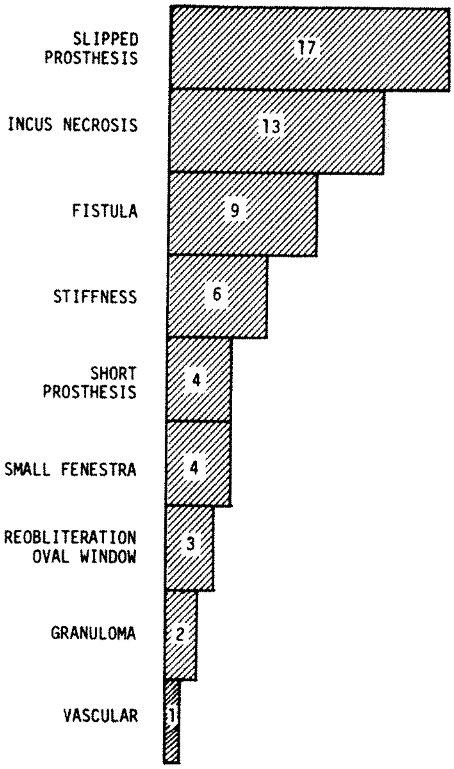

Fig. 2. Findings in 59 revision operations.

progressive sensorineural hearing loss of cochlear otosclerosis.

The records of 59 patients who underwent revision operations were examined in detail. In addition to those ears studied in Part 1, ears with a polyethylene and vein reconstruction were included. The most common diagnoses at revision operations (Fig. 2) were: 1) slipped prosthesis, 2) incus necrosis, and 3) oval window fistula; a distribution similar to that reported by Feldman and Schuknecht,[6] Dawes and Curry,[7] and Willis.[8] Table 7 tabulates the causes of failure with the presenting symptoms. The diagnosis at revision is correlated with the prosthesis type in Table 8. The most numerous types of failure are related with the incus necrosis, and medially, perilymphatic fistula. These will be dealt with separately.

SLIPPED PROSTHESIS AND INCUS NECROSIS

Oval Window Pathology. In both groups, although obliterated footplates were disproportionately frequent at the first operation, there was no evidence at the revision operation of secondary closure of the oval window in any case.

Prosthesis Type (Table 9). In half of the patients the most likely cause of disarticulation emerges from: 1) a his-

TABLE 7. CAUSES OF FAILURE AND PRESENTING SYMPTOMS FOR ALL PROSTHESIS TYPES COMBINED (N = 59)

	Deafness								
	Sudden								
		With V	*With T*	*With T & V*	*Gradual*	*Fluctuant*	*Vertigo*	*No Gain*	*No.*
Slipped prosthesis	6	2	0	0	5	2*	1	1	17
Incus necrosis	5	0	0	0	6**	0	0	2	13
Fistula	1	4	1	0	0	1	2	0	9
Excess small fenestra	0	0	0	1	3	0	0	1	5
Stiffness	0	0	0	0	0	0	0	5	5
Short prosthesis	1	0	0	0	0	0	0	3	4
Reobliteration oval window	0	0	0	0	2	0	0	1	3
Granuloma	0	2	0	0	0	0	0	0	2
Vascular	0	0	0	1	0	0	0	0	1
	13	8	1	2	16	3	3	13	59

*One with vertigo.
**Two with vertigo.
V - Vertigo; T - Tinnitus.

TABLE 8. FINDINGS AT REVISION OPERATIONS CORRELATED WITH OVAL WINDOW PATHOLOGY AND PROSTHESIS TYPE (N = 59)

	Oval Window Pathology			*Prosthesis*				
	Rim	*Biscuit*	*Obliteration*	*Polyethylene Strut*	*0.8 mm Teflon® Piston*	*0.8 mm Teflon® Wire Piston*	*Gelfoam® Wire*	*0.3 mm Teflon® Piston*
Slipped prosthesis	6	6	5	2	3	6	0	6
Incus necrosis	5	6	2	5	3	5	0	0
Fistula	7	2	0	0	1	5	2	1
Small fenestra	2	0	2	0	1	1	0	2
Stiffness	1	2	3	0	0	2	1	3
Short prosthesis	4	0	0	0	1	1	0	2
Reobliteration oval window	1	0	2	1	1	0	0	1
Granuloma	2	0	0	0	0	0	0	2
Vascular	0	1	0	0	0	0	1	0
	28	17	14	8	10	20	4	17

tory of barotrauma, and 2) unsatisfactory attempts at crimping the prosthesis as indicated in the surgical notes. Slippage occurred with 4.25% of 0.8 mm Teflon® wire pistons, 3.5% of polyethylene prostheses, 3.2% of 0.3 mm Teflon® pistons, and only 1.15% of standard 0.8 mm Teflon® pistons. The operation notes indicate difficulty in positioning the prosthesis in three ears, in whom hearing loss commenced from the onset in one, and after four and six months in the others.

Eight percent polyethylene and vein, 3.5% Teflon® wire and almost 2% of 0.8 mm all-Teflon® piston operations were complicated by incus necrosis. In 61% this occurred with prostheses which have previously been suspected of contributing to or causing incus necrosis due to their effect on the terminal part of the incus long process. Although the remaining third of cases had standard 0.8 mm Teflon® prostheses, in no instance was incus necrosis detected in association with the 0.3 mm Teflon® piston whose reduced mass and the less tight fit of its loop may provide an advantage in this respect over the 0.8 mm Teflon® piston.

Mode of Onset. The presenting symptom in all but two (slipped prosthesis) was hearing loss which occurred suddenly in about half of each group. Of the remainder with gradually developing hearing loss, several patients experienced various degrees of imbalance which may represent transient fistulas during displacement of the prosthesis.

TABLE 9. CORRELATION BETWEEN FINDING OF SLIPPED PROSTHESES AND INCUS NECROSIS AT REVISION OPERATIONS AND PERCENTAGE INCIDENCE AMONG EACH PROSTHESIS TYPE

			Prosthesis		
No.	*61*	*173*	*141*	*103*	*158*
No = 30	*Polyethylene Strut*	*0.8 mm Teflon® Piston*	*0.8 mm Teflon® Wire Piston*	*Gelfoam® Wire*	*0.3 mm Teflon® Piston*
Slipped prosthesis	3.5	1.15	4.25	0	3.2
Incus necrosis	8.2	1.70	3.5	0	0

Concomitant fluctuations in hearing would support this hypothesis.

In the 13 cases of incus necrosis, conduction hearing losses predominated (average 28 dB) but in three ears there were additional depressions in bone conduction thresholds of 10, 15 and 25 dB, only one of which subsequently fully recovered. In one patient who had a one-month history of purely sensorineural hearing loss with vertigo, although a fistula was suspected, the only finding at operation was incus necrosis.

Time Interval. The interval between the operation and onset of hearing loss due to disarticulation of the prosthesis from the incus averaged 1½ years. Alterations in middle ear air pressure while flying were probably responsible in one, and with upper respiratory infection in three. In three, it is questionable whether there was ever any postoperative gain. In none of the remaining seven patients could any cause be identified.

The time interval between the operation and the onset of hearing loss due to incus necrosis ranged from six months to eight years and averaged 3½ years. Not unexpectedly, the clinical effects of incus necrosis develop slowly.

RESULTS OF REVISION OPERATIONS

Slipped Prosthesis. An attempt to restore auditory function was made in each case at the second operation. The air-bone gap was closed or overclosed in 11 out of 17 (65%). Failure in the remainder consisted of a persisting conduction problem in three and gross cochlear dysfunction in three more, in all of which the secondary oval window membrane was incised to receive a new prosthesis.

Incus Necrosis. In five, another prosthesis was articulated with the shortened long process: in four, a malleus to oval window Teflon® piston was used, and in four a direct tympanic membrane to oval window columella (three homologous nasal cartilage, one porous polyethylene) was used. So far, in a follow-up ranging from six months to 12 years (average 5 years), no evidence of further ossicular necrosis nor of rejection, has been detected.

Seven of these 13 ears have overclosed their air-bone gap and three more have closed it to zero (77% "success"). In one other ear (malleus to oval window piston) the conduction hearing loss has persisted and in two others (0.8 mm Teflon® piston to oval window) the result is unsatisfactory due to depression in bone conduction averaging 15 and 25 dB through the frequencies 0.5 - 4 kHz.

DISCUSSION

Seventy-five percent of the *slipped prostheses* were those whose articulation requires considerable skill, such as wire-loop types with their inherent crimping problems. Ludman[9] suggests that slippage is commonly due to the wire being crimped onto the long process so that the angle between the shaft and the crook is obtuse. Subsequently, as a membrane forms across the oval window and moves laterally it may push the piston off the long process. With the standard 0.8 mm Teflon® piston, lateral movement is resisted by the extra spur of Teflon® that continues the crook past its union with the shaft. On the other hand, the delicacy of the 0.3 mm Teflon® piston offsets this advantage. The findings at revision suggest that overopening the loop, which destroys its powers of self-restoration, was the reason for slippage. Imperfect articulation must predispose to prosthesis slippage, especially in the event of a sudden change in the ratio of middle ear to environmental air pressure, or due to an increase in perilymphatic pressure.[10]

Although *incus necrosis* has been reported with practically every kind of prosthesis, it has occurred most commonly in this series with prostheses made from either polyethylene tubing or stainless steel wire. Our experience of one case taking as long as eight years to declare itself, suggests that this can be a slowly developing process. It is interesting to note that although there was a history of head trauma in two instances, this, because of the time re-

TABLE 10. CORRELATION BETWEEN FINDING OF FISTULA AT REVISION OPERATIONS AND PERCENTAGE INCIDENCE AMONG EACH PROSTHESIS TYPE

			Prosthesis		
No.	*61*	*173*	*141*	*103*	*158*
No = 9	*Polyethylene Strut*	*0.8 mm Teflon® Piston*	*0.8 mm Teflon® Wire Piston*	*Gelfoam® Wire*	*0.3 mm Teflon® Piston*
Fistula	0	0.6	3.5	1.9	0.6

lationship, probably did nothing more than complete an already established pathological state. In no case was there concomitant secondary osseous closure of the oval window. In all the failures with the newly created sound conduction mechanism detected in this series, loss of early hearing gain has been the predominant clinical presentation: in half this has been sudden, and in the other half it has developed gradually. When there has been fluctuation of hearing, this has been accompanied by vertigo.

An incidence of one in four patients with vertigo as a consequence of prosthesis disarticulation as compared to one in six with incus necrosis suggests that necrosis is a more gradual process than dislocation, and is due to a slowly progressive lateral movement of the oval window membrane which, while avoiding a fistula, inevitably erodes the incus because of pressure necrosis. This is in line with the theories of Ludman[9] *(vide supra)* and Shea[10] regarding eversion of the lining membrane of the vestibule caused by the considerable fluctuations in cerebrospinal fluid and perilymphatic pressures which occur routinely during physical activity.

Although the frequent association between prosthesis problems and obliterative otosclerosis suggests that regrowth of bone in the oval window might have contributed to the incidence of eventual failure, this was not confirmed at any revision operation.

Several authors have reported unsatisfactory hearing results following revision operations.[6,7,11] The results in this series were much more encouraging in that almost three out of four operations succeeded in restoring the original hearing gain. Revision operations should be undertaken not only to rule out the possibility of a perilymph fistula but also to give the patient the possibility of regaining his earlier functional improvement. It is our conclusion that avoidance of prosthesis slippage and incus necrosis depends upon the choice of prosthesis and the skill with which it is used. Although the 0.3 mm Teflon® piston may be more difficult to articulate with the incus than other prostheses and may fail because of subsequent slippage, this disadvantage is relatively easily corrected and is far outweighed by the absence of complications such as incus necrosis.

PERILYMPHATIC FISTULA

Surgical Factors. A comparison of the incidence of fistula for each kind of prosthesis (Table 10) shows a significantly greater incidence with the 0.8 mm Teflon® wire prosthesis.

In more than half (five ears) the fenestra was created by removing half or more of the footplate and in three others, the footplate was removed completely. Thus, in eight out of nine ears, fistula has occurred after large fenestra stapedectomy (LFS), whereas in only one ear has there been a fistula in small fenestra stapedectomy (SFS) using a 0.3 mm Teflon® piston.

The type of oval window pathology did not appear to predispose to the development of fistula.

Mode of Onset (Table 11). This was less clearcut than with the complications affecting the outer end of the prosthesis. In just over half (five ears) the presenting symptom was a sudden loss of hearing and in three of these there was also imbalance or vertigo. Of the

TABLE 11. CORRELATION BETWEEN PROSTHESIS TYPE AND CLINICAL FINDINGS IN FISTULA CASES (N = 9)

		Presentation						*Outcome*					
		Hearing Loss			*V*	*Imb*	*T*	*Hearing*			*V*	*T*	
P	*Prosthesis*	*On-set*	*dB↓BC*	*Sp%↓*				*R*	*I*	*W*			*Follow-up (yr)*
1	0.3 mm Teflon®	S	10	0	+	—	—	+					½
2	0.8 mm Teflon® wire	G	40	16	—	—	—		+		+		5
3	Gelfoam® wire	—	0	0	+	—	—		+				5
4	0.8 mm Teflon® wire	F	10	0	—	+	—		+		+		7
5	Gelfoam® wire	S	15	16	—	+	—	+				+	3
6	0.8 mm Teflon® wire	—	0	0	+	—	—	+				+	8
7	0.8 mm Teflon® wire	S	20	24	—	—	—	+					5
8	0.8 mm Teflon®	S	40	26	—	+	—			+			1
9	0.8 mm Teflon® wire	S	10	12	—	—	—	+					½

S - Sudden; G - Gradual; F - Fluctuant; R - Restored; I - Intermediate; W - Worse; Imb - Imbalance; V - Vertigo; T - Tinnitus.

+ - Present.

Sp% - Speech discrimination score.

remainder there was gradual hearing loss in one and fluctuant hearing in another, while in two others (Patients 3 and 6), vertigo, of sudden onset, without auditory symptoms, signaled the occurrence of fistula. Pressure change may have been the cause in one patient who experienced sudden hearing loss during air flight and in another who presented primarily with vertigo, following several hours of unusual physical exertion.

In the six patients whose initial symptom was hearing loss, this was sensorineural in type and averaged 20 dB, with an appropriate deterioration in speech discrimination. Quite different was the experience of the three patients who suffered acute vertigo; in two there was no change in bone conduction thresholds or speech discrimination, and in the third bone conduction was worse by no more than 10 dB, with no loss of speech discrimination.

In marked contrast with the other groups requiring revision operations, sensorineural rather than conduction hearing loss was the predominant feature of fistula. However, it should be noted that in three patients there was an additional conduction loss of 20 dB in two and 10 dB in one.

Time Interval. The time interval between the primary operation and the onset of hearing loss or acute vertigo averaged four years with a range of two to six years.

The operation notes indicate the following findings associated with fistula:

1. A defect in the oval window membrane through which perilymph was seen to be escaping in four, a leak around a wire prosthesis in two, and around the margins of a Teflon® piston in two. In one other, although the leak was profuse, its origin could not be ascertained.
2. In two, there was also incus necrosis, in another there was an oval window granuloma and in one other with a history of recent head trauma, an 0.8 mm Teflon® wire piston was only loosely connected with the long process of the incus.

RESULTS OF REVISION OPERATIONS

Hearing. Although the aim of the second operation in this group of patients was primarily to identify an oval window fistula and to terminate the perilymph leak, it was also designed to restore hearing.

In four ears where the oval window was regrafted with vein and an 0.8 mm

Teflon® piston placed on it with surrounding Gelfoam® packing, there was restoration of air and bone conduction thresholds and speech discrimination in three and an improvement to within 10 dB of the previous bone conduction levels for the speech frequencies in the other. In three ears where a flap of mucosa from the promontory was reversed over the oval window and covered with vein and an 0.8 mm Teflon® piston[12] there was a complete return to the postoperative hearing level in one and improvement to within 10 dB of the previous bone conduction thresholds in another, but in the third, although hearing improvement did occur, the average bone conduction threshold was still 40 dB worse than originally. In one other ear the replacement of a previous 0.8 mm Teflon® wire piston with a Gelfoam® and wire prosthesis, produced an improvement to within 10 dB of the previous bone conduction level.

In another revision, where the leak was not profuse, the previous 0.8 mm Teflon® wire piston was packed around with Gelfoam®, with a complete restoration of hearing.

In summary, a second operation succeeded in restoring the hearing loss due to fistula in five and in considerably improving it in three. Only one ear remained permanently affected.

Vertigo. Following the second operation, imbalance was completely eliminated in five of the six patients in whom this symptom had been present prior to the second operation. The sixth patient in whom a Gelfoam® and wire prosthesis was used at the second operation continues to have minor positional vertigo periodically (further exploration was negative).

Tinnitus. Although this symptom was relieved in the only patient in whom it was present prior to the second operation, in two others it developed following revision.

The follow-up period in this group averaged four years with a range of two to eight years.

DISCUSSION

Harrison et al[12] defined the experience of many North American surgeons by stating that fistula was the outstanding problem in stapes surgery – this in contradistinction to European authors who have expressed a greater concern with the problems of cochlear degeneration. Indeed, Dawes and Curry[7] have rarely detected any case of fistula at revision, and Marquet et al[4] reported 1,550 cases with no fistula when using a piston with a "small hole" in the footplate and no viable graft material.

While surveying the cases of fistula in 3,500 stapedectomy operations, Harrison et al[13] did not find a significant correlation between this complication and the surgical technique, but in a later paper[14] they indicated that the incidence appeared to increase with time for all techniques and was as high as 3.8% with the 0.8 mm stainless steel piston. In itself, in our experience, the predominance of rim otosclerosis was probably not directly a significant factor in the causation of fistulas because it is much the most frequent type of pathology. Nevertheless, this kind of footplate may indirectly influence the outcome of stapedectomy in that it facilitates LFS. Eight of the nine fistulas in this series were complications of LFS operations. Hearing loss of sudden onset especially when accompanied by vertigo or acute vertigo after stapedectomy, are highly significant diagnostic symptoms of fistula of the oval window. A history of factors likely to cause a pressure differential between the inner and middle ear is more in favor of a diagnosis of fistula than incus necrosis or dislocated prosthesis.[14]

The value of vertigo per se as a diagnostic symptom is debatable. Harrison et al[12] and Douek[15] have referred to the difficulty in differentiating between fistula and endolymphatic hydrops, and it is possible that disturbance of the normal perilymph-endolymph volume relationship may be common to both. The significance of vertigo was also discussed by Goodhill[16] who stated that many of his patients had experienced intermittent imbalance for years following stapedectomy before a fistula was eventually diagnosed. On the other hand, Willis,[8] McCabe[17] and Hough[18] all considered that the frequency of disequilibrium among otosclerotics prior to any form of stapes operation diminished its value in reaching a diagnosis.

The fact that in this series a fistula has not been found to be present at revision operations for incus necrosis or a slipped prosthesis, suggests that when the prosthesis migrates from the oval window in man there is a similar healing potential of the oval window as that demonstrated in the experimental animal.[19] This tendency presumably also exists in patients while they are in a state of rest during the first days after operation. and usually permits rapid closure of the immediate surgical fistula. On the contrary, when at some time after the oval window has healed, an abrupt pressure differential between the perilymphatic and mesotympanic spaces ruptures the oval window membrane, then the continued presence of a foreign body in the oval window is likely to prevent its healing.

Regardless of the significance of vertigo as a diagnostic feature, when hearing loss, either conductive or perceptive, of sudden or gradual onset, develops, the possibility of a fistula must always be taken into account and the need for an exploratory operation seriously considered. Careful observation and interpretation is essential for the correct timing of tympanotomy and the decision, if and when to intervene, should be based primarily on the audiometric response. We suggest that an overall bone conduction loss of 10 dB (averaged through the four speech frequencies) or a reduction of the speech discrimination score by 10% or more should be considered an alert warning sign; any greater loss in function should be considered an absolute indication for immediate reoperation.

In our experience, as with Dovek,[15] revision operations have not proved as dangerous to hearing as others have warned.[7,11,12,20,21] In fact, Dawes and Curry[7] are so concerned about the risks of reoperation that they advocate operating on the other ear instead! Obviously, without unoperated "controls" we cannot know the outcome of not operating. What we do know is that following revision, the function of five of nine ears in this series was fully restored; considerably and usefully improved in three; leaving only one patient (10%) whose hearing, unfortunately, was not altered but in whom nevertheless vertigo has been eliminated.

The reason for a greater degree of success with revision operations for fistula in this series as compared to some reported elsewhere would appear to be a technical one. Following LFS the better matched the character of the neo-oval window membrane to its stresses, the more successfully will it act as a seal. It is generally agreed that connective tissue, be it vein or perichondrium, provides the best means of preventing a fistula.[5,18,22] It therefore appears reasonable to use these materials for the repair of a fistula to minimize the chance of recurrence. The results of reoperation using vein graft in this series are in accord with those obtained by Harrison et al[12] using connective tissues and much superior to those which followed, covering the fistula with nothing more than Gelfoam®.[8]

It is worth noting that the diagnosis of fistula in many of the patients who presented with hearing loss as their predominant symptom could have been made by the light of hindsight on the basis of the type of hearing impairment because, on the whole, mainly perceptive losses were associated with fistula while mainly conductive losses were due to disarticulation of the lateral end of the prosthesis. Nevertheless, the observation of Goodhill[16] that conduction loss may be the only early manifestation of fistula should certainly not be ignored. Although concomitant vertigo certainly supports the diagnosis of fistula, this symptom was not exclusively associated with the phenomena and cannot be relied on as a definite indication of its presence. It should be noted especially that fistula has been diagnosed in only one ear in this series when SFS was performed, representing an incidence of 0.7%, with the 0.3 mm Teflon® piston.

REMAINING DIAGNOSES

The remaining diagnoses at revision operations together comprise no more than one-third of the total and include:

1. Short prosthesis.
2. Small fenestra.
3. Ossicular stiffness.
4. Reobliteration of the oval window.
5. Granuloma of the vestibule.
6. Presumed inner ear lesion (? vascular).

The first three categories represent technical errors and they and category 4 characteristically presented as failures to overcome or as an early reoccurrence of conduction hearing loss. When these causes for failure were detected, our attempts to put matters right were successful in two-thirds. Although the findings in two patients with proven granuloma do not provide data of statistical significance, they are of interest. One case was similar to those described by Kaufman and Schuknecht.[23]

This patient with rim otosclerosis had SFS using an 0.3 mm diameter Teflon® piston. The operation took 12 minutes and was described in the operation notes as "atraumatic." From the first postoperative day there was persistent vertigo and ataxia and at five days postoperatively an average 15 dB depression in bone conduction and a reduction of 20% in speech discrimination, findings which persisted until the revision operation was performed 16 days after the first. The prosthesis was surrounded by a spherical mass of granulation tissue about 4 mm in diameter. There was no evidence of fistula. When the granulation tissue which was seen *not* to enter the vestibule was removed, a dramatic yellow discoloration of the perilymph was noted. The remaining large portion of footplate was then extracted, and after covering the oval window with a piece of compressed vein, an 0.8 mm Teflon® piston was placed between the vein and the incus. Almost immediately vertigo ceased and one month later there was overclosure of the air-bone gap and an improvement in speech discrimination from the original preoperative level (88%) to 100%.

The second granuloma case was one in which the findings were less typical in that a granuloma was found to be accompanied by a perilymphatic fistula at a revision operation carried out four years after the original procedure because of recurrent vertigo and hearing loss. The statistics of this patient who did well after her revision operation are included in the fistula group. In addition, there were three patients in whom fistula being suspected, but not confirmed at revision, all recovered their original hearing and balance. Retrospectively, these three and one other who experienced sudden hearing loss accompanied by vertigo and tinnitus six months postoperatively (and in whom no fistula or other abnormality was detected at revision and who did not recover), cannot be categorized. In our opinion, this patient probably suffered a vascular cochlear defect. The lesion in those three who recovered appears more likely to have been a temporary fistula than endolymphatic hydrops (usually a recurrent condition) because there have been no further symptoms (range two to nine years, average follow-up of 3.5 years).

SUMMARY AND CONCLUSIONS

1. At presentation, above all, loss of a satisfactory initial hearing gain is the sign and symptom of fistula, slipped prosthesis and incus necrosis. Immediate failure to overcome a previous conduction loss usually indicates a surgical technical error.

When the onset of delayed hearing loss is *abrupt* (57%), there is an equal chance that any one of the three main causes will be found, whereas when it is gradual, complications at the lateral end of the prosthesis are likely (11 out of 12 ears). Neither fluctuant hearing nor vertigo are of special diagnostic significance.

2. Small fenestra stapedectomy operations were complicated much less frequently (3.8%) than all wire loop prostheses (7.3%) and very much less frequently than 0.8 mm Teflon® wire pros-

theses (11.2%: $P < 0.05$) by factors directly related to the piston (those failures due to malleus fixation and technical failure such as too inadequate fenestra as compared to piston diameter and too short prosthesis being considered irrelevant).

3. If one case of fistula in which granuloma was probably the prior pathology is disregarded, then it can be seen that the 0.3 mm Teflon® piston has emerged as the only prosthesis not responsible for prosthesis rejection in this series. When this prosthesis is used in SFS, additional factors in its favor are, a) depth of penetrance into the fenestra is easily judged due to the proximity of the piston to the fenestra edge, and b) the small dimensions of the opening around the piston restrict the passage of perilymph and contaminants and enhance rapid membranous closure of the surgical defect.

It appears that the only criticism which can be fairly applied to the 0.3 Teflon® piston on the basis of the statistics of this series concerns the incidence of slipped prosthesis due to technical problems in articulating the prosthesis with the incus, and the less efficient performance at the speech frequencies.

On the evidence available from this part of our research, we conclude that SFS operations with a 0.3 mm Teflon® piston are the least likely to be complicated by problems which seriously threaten the auditory status of the patient.

PART 3: INCIDENCE AND ETIOLOGY OF SEVERE SENSORINEURAL HEARING LOSS FOLLOWING STAPEDECTOMY

INTRODUCTION

In stapedectomy the fate of the inner ear is most threatened by the events which occur when the oval window is fenestrated. The theoretical possible sources of labyrinthine damage are numerous and include:

Immediate Causes.

1. Excessive movement of all or part of the stapes, usually during attempts to remove a prematurely mobilized footplate, or prolonged manipulation of an oval window soft tissue of Gelfoam® graft, both causing a hydraulic effect.

2. Rupture of the membranous inner ear by attempts to remove pieces of footplate from the vestibule.

3. Distortion of the membranous inner ear arising out of sudden decompression of the vestibule of the inner ear by rapid loss of perilymph, usually because of injudicious use of suction, but occasionally in ears with an abnormally patent cochlear aqueduct.

4. Acoustic trauma from instrumentation, usually drilling in obliterative otosclerosis.

5. Presence of blood in either or both fluid compartments.

Delayed Causes.

1. Damage to the utricular macula from impingement of an overlong prosthesis.

2. Hydrops of the scala media due either to prolonged perilymph loss owing to delayed healing of the oval window, or due to sudden rupture of the periprosthetic membrane at some time after the operation (fistula).

3. Slowly progressive hair cell degeneration in the basal turn, suspected to be a basic but varied consequence of all types of stapes operation.

The reported incidence of "dead" ears within one month following stapedectomy varies from 0.5 to 4%. Unfortunately, it is not possible to determine from most reports how many "dead" ears are due to trauma at the time of operation and how many are the result of late complications such as perilymphatic fistulas. In addition, it is well-recognized that the proportion and duration of follow-up in many reported series is insufficient to reflect the actual incidence of complications. Because this series, although small, has been followed-up consistently and almost totally, it was felt that its analysis should provide an accurate estimate of the risks of sensorineural hearing loss in stapedectomy. To this end, the clinical and surgical records of all those patients who experienced depression of averaged bone conduction thresholds (0.5 - 4 kHz)

TABLE 12. TRAUMATIC FACTORS DURING OPERATIONS ASSOCIATED WITH IMMEDIATE SENSORINEURAL HEARING LOSS

Excessive perilymph loss		10
Perilymph loss & hydraulic		8
"Floater" footplate	6	
"In toto" footplate removal	2	
Secondary oval window fenestration		3
Drill out		2
Wasserman +		1
Nil		1
Immediate sensorineural loss		25 (3.5%)

by 20 dB or more or a reduction in speech discrimination of 20% or more, were scrutinized. There were 25 in whom a sensorineural hearing loss has been present since the time of operation, and 4 in whom the onset was delayed.

FINDINGS

Immediate Sensorineural Hearing Loss. This disaster befell 25 of the 713 ears in this series (3.5%). The records indicate that in 18 of these 25 ears events considered by the surgeon likely to be traumatic occurred during the operation (Table 12). These were excessive perilymph loss due to difficulties in removing the footplate (ten cases); and combined hydraulic effects on the labyrinth and excessive perilymph loss (eight cases) due to total over-early footplate mobilization ("floater") (six cases) and removing the whole stapes as one unit (two cases).

The cause of hearing loss may have been of a similar nature in three ears where immediate cochlear dysfunction followed a revision operation in which a new piston was inserted through an incision in the membrane formed after prior large fenestra stapedectomy (LFS). Whether the membranous labyrinth was adhesed to the oval window membrane and was inadvertently incised is not known. Thus, in these 21 ears it appears possible that excessive pressure changes in either direction due to hydraulic compression or loss of perilymph may have created a fatal disequilibrium between the endolymphatic and perilymphatic compartments.

In three other ears the relationship of trauma to the end result is less certain, but is likely in two where prolonged drilling occurred. In the third, a positive Wassermann reaction suggests that in this ear a poverty of reserve existed.* In the remaining ear the procedure was described as "atraumatic" in the operation notes.

In summary, trauma to the inner ear appears likely to have influenced the outcome in 23 of these 25 operations (92%) Since "traumatic factors" were a feature of only 155 of the 688 operations (23%) in which immediate severe sensorineural hearing loss did not occur, it is concluded that inner ear trauma, especially that due to alterations in perilymph pressure, plays a major part in the causation of irreversible cochlear damage in stapedectomy ($X^2 = 58.5$, $P < 0.001$).

Delayed Sensorineural Hearing Loss. There were four other ears in which an audiometrically confirmed early hearing improvement was lost suddenly and did not return (0.6%). In three the loss was total: one occurred at one month after an operation which had been complicated by a floating footplate (exploration was negative); one occurred at six months postoperatively (exploration was negative); and in the other, sudden hearing loss occurred during an upper respiratory infection five years after operation (no exploration was performed). In the fourth ear in which the posterior half of the footplate had been lost in the vestibule, the loss, occurring suddenly at four years, was evenly distributed through the speech frequencies at 60 dB, with an accompanying fall in speech discrimination from 92 to 44%. The hearing level has changed little during the four years since. The part played by surgical trauma cannot be assessed in these four ears.

It should also be noted that all of

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*A retrospective history strongly suggested that syphilis had been contracted two years preoperatively. Serological tests were carried out postoperatively.

TABLE 13. PERCENTAGE INCIDENCE COCHLEAR LOSS >20 dB IN REGARD TO AGE, PREOPERATIVE BONE CONDUCTION AND OVAL WINDOW PATHOLOGY

Age		*<50 years*			*>50 years*		
*Preoperative bone conduction**		*A*	*B*	*C*	*A*	*B*	*C*
Oval window pathology	Rim	1.5	4	0	3	0	0
	Biscuit	5	7.5	14	0	17	35
	Obliteration	9	6	0	15	22	29

*Shambaugh groups A, B, C.

these 29 (immediate and delayed) severe sensorineural hearing losses occurred after LFS; none followed small fenestra stapedectomy (SFS). Eighty-three percent were total hearing losses ("dead" ears) and the remainder, with flat or sloping audiograms, had such a loss of discrimination that their hearing was virtually useless, although they retained some low tone perception. Thus, we are aware of an overall incidence of severe sensorineural hearing loss in 4% of our patients so far. Nevertheless, although surgical traumas appear to play such an important role in the causation of cochlear damage, the fact remains that as many as 25% of the cochleas in this series survived such factors, apparently unharmed. Thus, it would appear that while most otosclerotic ears can survive the stresses due to alterations in fluid pressure and concurrent membranous distortion which inevitably must occur during carefully performed stapedectomy, there are certain ears which are rendered less resistant by predisposing factors.

Hoping to find an explanation for these cases of severe sensorineural hearing loss which might provide a means of identifying patients who were unsuitable for operation, we considered other factors which might contribute to the development of severe postoperative sensorineural hearing loss in this series. The incidence of severe sensorineural loss in regard to age, preoperative bone conduction (Shambaugh groups A, B and C) and oval window pathology was examined (Table 13).

PREOPERATIVE BONE CONDUCTION THRESHOLDS. The ability of any organ to withstand trauma will be related to its reserve function. Because it appeared likely that measurable loss of function would reflect a degree of preexisting cochlear deficiency approaching its reserve and that this might indicate a predisposition to further loss in the face of surgical trauma, a comparison of the relative incidence of hearing loss within the Shambaugh groups was made. This showed a very significant susceptibility to postoperative dysfunction ($X^2 = 14.49$, $P < 0.001$) when the preoperatively averaged bone conduction threshold was 40 dB or worse (Shambaugh group C).

OVAL WINDOW PATHOLOGY. Because surgical skill must be equal to the technical difficulties posed by the type of footplate for a successful outcome in stapedectomy, a relationship between the incidence of severe sensorineural hearing loss and footplate pathology was sought. Our analysis showed that overall the risk is significantly greater with obliterative and biscuit otosclerosis than with rim otosclerosis ($X^2 = 13.84$, $P < 0.001$).

AGE. On the basis that degenerative processes which might contribute to the incidence of severe sensorineural hearing loss by rendering the cochlea more fragile are often age-related,[24] this series was divided arbitrarily into those patients aged less than and those aged more than 50 years.

Although it was found that the incidence of severe cochlear dysfunction was not significantly higher in the older age group ($X^2 = 1.47$, $P > 0.5$) *overall*, further analysis provided additional information about causative factors related to age which have considerable clinical importance.

1. In the under 50 age group the risks inherent in operating on rim otosclerosis

TABLE 14. DISTRIBUTION OF SEVERE HEARING LOSS BY DEGREE OF RISK

	Severe Loss	*Other*
High risk Patient > 50 years with type C Shambaugh or obliterative otosclerosis	10	43
Low risk All other patients	15	582

$X^2 = 30.93$ ($P < 0.001$).

are less than with other types of disease ($X^2 = 6.19$, $P < 0.05$) whereas, in the over 50 group the significance of the risk with rim otosclerosis is very much less than with obliterative and biscuit footplates ($X^2 = 11.83$, $P < 0.005$).

2. Under 50, the preoperative auditory function does not affect the outcome ($X^2 = 1.62$, $P > 0.05$), whereas over 50, the risks of a "dead" ear in Shambaugh group C patients is high ($X^2 = 12.64$, $P < 0.01$).

When age, oval window pathology and the audiogram were related to the overall outcome, it is seen that patients aged 50 or more, with either a type C Shambaugh bone conduction threshold or obliterative otosclerosis, ran a one in three risk of severe sensorineural loss in this series ($P < 0.001$) (Table 14).

In the hope that a formula as suggested by Sheehy[25] which would predict "at risk" patients preoperatively might be constructed, the distributions of age group, preoperative bone conduction and oval window pathology in the series as a whole were studied (Table 15). It was not found that any of these factors, either singly or in combination, provided any useful evidence of unsuitability for operation.

PROSTHESIS TYPE (TABLE 16). The possibility that the material of the prosthesis or the technique for its insertion might be relevant was considered. Although a high incidence of immediate sensorineural loss with the Gelfoam® wire prosthesis and the polyethylene tube was noted, it would be dangerous to draw any firm conclusions for two reasons:

1. The dexterity of both surgeons was probably less in the early part of the series when the polyethylene tube technique was used almost exclusively.

2. The high incidence of cochlear dysfunction with Gelfoam® wire prosthesis is likely to be influenced by the fact that these operations were all total stapedectomies and many carried a threat of trauma because in all there was greater than usual difficulty in managing the footplate.

Although it is suspected that the incidence of delayed sensorineural loss might be affected by techniques more liable to fistula, we have insufficient evidence to decide.

DISCUSSION

Incidence. There is a noticeable difference in the reported incidences of severe sensorineural hearing loss following stapedectomy. On one hand, Willis[8] in discussing complications, does not report immediate hearing loss in any of his patients, and Dawes and Curry[26] reporting on 351 piston operations, list only one immediate and only one delayed sensorineural loss. Similar statistics are published by Kaufman and Schuknecht[23] and Sooy et al.[27]

On the other hand, Ludman and Grant[2] reported 15 "dead" ears in 176 cases (6%). Eight had an early onset (3.4%), and seven (2.9%) occurred more

TABLE 15. TOTAL SERIES: PERCENTAGE DISTRIBUTION FOR AGE, PREOPERATIVE BONE CONDUCTION AND OVAL WINDOW PATHOLOGY

Age		*<50 years*			*>50 years*		
Preoperative bone conduction		A	B	C	A	B	C
Oval window pathology	Rim	29	13	2	5.5	8	3
	Biscuit	12.5	6	2	4	2.5	1
	Obliteration	3	2.5	0.5	2	1	1

TABLE 16. INCIDENCE OF SEVERE SENSORINEURAL LOSS WITH EACH PROSTHESIS TYPE

		Prosthesis						
	No.	*61*	*173*	*141*	*103*	*158*	*10*	*1*
		Poly-ethylene Strut	*0.8 mm Teflon® Piston*	*0.8 mm Teflon® Wire Piston*	*Gel-foam® Wire*	*0.3 mm Teflon® Piston*	*Malleus Foot-plate Pros-thesis*	*Wire Vein Prosthesis*
No.	Immediate	4	5	3	9	0	3	1
	Delayed	0	1	0	3	0	0	0
%	Immediate	6.6	2.9	2.2	8.7	0	30	0
	Delayed	0	0.6	0	2.9	0	0	0

than two years after operation, three after more than six years.

Our experience, 3.5% with immediate and 0.4% with delayed onset, lies somewhere between these extremes. With so many variables of such considerable degree as surgical dexterity, selection of patients and the durations of follow-up as exist, further discussion about the incidence of profound sensorineural hearing loss after stapedectomy is not likely to be meaningful.

Trauma. Most of those who have written about sensorineural hearing loss following stapedectomy have concentrated on *traumatic factors* during or immediately after the operation and most of the advice which is given concerns matters of surgical technique.

Hardcastle and McGee[28] list some of the factors which are likely to contribute to cochlear impairment after stapes operations including:

1. Techniques requiring opening of the labyrinth.
2. Choice of prosthetic material.
3. The use of the drill on fixed footplates.
4. The presence of blood or bone dust in the labyrinth.
5. The effects of mechanical injury to the membranous duct.
6. The sudden movement of a previously fixed footplate.

Various authors have laid special emphasis on one or other of these. Hough[18] underlines the importance of early fenestration to admit the insertion of an instrument medial to the stapes footplate and states that drilling is dangerous in obliterative otosclerosis, whereas Ludman[9] has not found the drill a significant factor in cochlear loss. Our experience does not support the view that the average cochlea is at any increased risk during drilling or while removing a floating footplate, provided the utmost care is exercised.

Hardcastle and McGee[28] investigated hydraulic effects on the cochlea during stapedectomy and concluded that the likely causes of high tone sensorineural hearing loss are not so much related to changes in perilymphatic fluid due to sudden movement of the stapes but were the result of compression of the saccular endolymphatic fluid by the inward subluxation of the stapes during its removal. The presence of adhesions between the membranous labyrinth and the footplate may account for cochlear damage in those cases where no subluxation occurred. Again, although the main purpose of House et al[29] was to prove that techniques which avoided removal of any part of the footplate were safer, and that this especially applied to the "fragmentation" technique, they also referred to the possibility (based on histological evidence) that because of adhesions, removal of the posterior half of the footplate might occasionally traumatize the membranous labyrinth.

Although there have been few reports to support the opinion of Kaufman and Schuknecht[23] regarding granuloma as a cause of "dead" ear, this may well be due to the fact that reoperation as an emergency measure when patients are failing to gain hearing postoperatively is not routinely carried out in most centers. Certainly, this comment must apply to our series.

Although Linthicum and Sheehy[30] could find no evidence that blood entering the vestibule during stapedectomy had any detectable serious consequences, the possibility of labyrinthine trauma from this cause cannot be dismissed. There is ample evidence from studies of the temporal bones of patients suffering from hemopoietic disease who experienced sudden severe perceptive hearing losses shortly before death that contamination of the inner ear fluids by the various components of blood (potassium ions, protein, etc) can grievously affect the structures of the inner ear.[31] Furthermore, Simmons[32] has postulated an association between hydraulic effects and intralabyrinthine hemorrhage.

Age. Hammond[33] believes that increasing age is not a contraindication and has not discovered any increased risk in patients over 60, and Schuknecht,[34] although he delays operation until the age of 20, states that he has no upper age limit. By contrast, Owens et al,[35] on the basis of changes in speech discrimination, concluded that patients aged more than 60 had a greater risk of cochlear degeneration as a result of stapedectomy. Again, Siirala et al[36] found that the best results were obtained in patients aged between 30 and 60.

By contrast, our findings indicate a highly significant relationship between postoperative sensorineural hearing loss and aging when other factors are also considered. This difference could be due to the depth of our analysis which evaluated the ability of the ear to withstand trauma on the basis of its preoperative function, the type of oval window pathology and the size of oval window fenestration.

A significantly greater incidence of postoperative sensorineural hearing loss in the older age group when the preoperative hearing level was Group C Shambaugh clearly puts older patients in an at risk category, a hazard which is even greater when there is also biscuit or obliterative otosclerosis. We argue that the most likely explanation for the difference in preoperative cochlear function between the young and the old is a vascular one, regardless of whether or not this is part of more general circulatory disease or an accumulative response to noise, tobacco, diet or any other of the suspected contributors to "presbycusis." In addition, or as a separate alternative, poorer cochlear function in the older age group may be due to involvement of the cochlea by the advance of otosclerotic foci which, by virtue of their effects may very well be the primary cause of preoperative sensorineural hearing loss.[37-39] Regardless of why cochlear function deteriorates more rapidly with age in otosclerosis, there is undoubtedly a greater susceptibility to adverse factors deriving from surgical treatment.

Although "surgical" causes appear to account for most of the sensorineural hearing losses complicating stapedectomy in this series, none proved to be significant on its own. However, there was "trauma" in a significantly greater portion of these immediately deafened ears than in the series at large ($P < 0.001$) and thus the conclusion that trauma causes sensorineural hearing loss in the susceptible cochlea appears to be inescapable. Lawrence et al[40] demonstrated the vasospastic effect of noise on the vessels of the basilar membrane. Their findings are supported by results of other experimental studies which measured the effects of noise and intracochlear histamine on the cochlear microcirculation[41] and the effects of noise on endolymphatic potassium-sodium balance.[42] By inference, we suggest that the introduction of mechanical energy to the inner ear from any source causes reduction in microcirculatory flow which may lead to hypoxic degeneration of the organ of Corti and that this may be further aggravated by humoral means through the release of histamine[41] We therefore propose that such is the mechanism whereby severe sensorineural hearing loss occurs when the trauma which is inevitable in any stapes operation exceeds the limits of tolerance of the ear in question.

The fact that there were no cases of severe inner ear damage following 140 SFS operations as compared with 29 out of 427 LFS operations provides overwhelming support for our thesis that SFS is the technique least liable to serious complication.

Clearly there is much opinion to support SFS, even if the reasons for doing so are not always the same.

CONCLUSIONS

1. Surgical trauma has been a significant factor in the development of immediate or sudden sensorineural loss following stapedectomy.

2. Preoperative cochlear impairment, obliterative otosclerosis and increased age all independently increase the risks of postoperative cochlear dysfunction. This may be due to associated changes in vascular status and the additional possibility of advanced *cochlear* otosclerosis, both of which are likely to be reflected in the audiometric pattern. Therefore, older patients in the Shambaugh type C group must be considered in an at risk category, especially when an obliterated oval window is found at operation. It would therefore seem sensible to avoid stapedectomy in these patients, remembering that as in all forms of otosclerosis, a hearing aid can frequently offer a great deal and carries no risk of worsening the auditory status.

3. Under no circumstances should the other ear be operated upon when the first ear has suffered a significant cochlear loss because the possibility of delayed total hearing loss in this ear can never be ruled out. This is because both ears are likely to be affected by the same problems initially during the operation, because of the high incidence of symmetrical footplate pathology[2] and also permanently thereafter because the threat of upper respiratory infection and abrupt changes in atmospheric and cerebrospinal pressure are always likely to affect *both* ears.

4. An operation which limits trauma to the minimum should be used in every case. Thus, all large fenestra techniques are to be avoided if possible. Wide removal of the stapes footplate must predispose to contamination of the vestibule by bone duct and blood, produce a large hydraulic effect in the vestibule of the inner ear, lead to prolonged perilymph drainage and threaten the vascular sufficiency of the membranous labyrinth.

5. Nonoccurrence of severe sensorineural hearing loss in any ear treated by the SFS technique in this series supports the claim that this operation carries much less risk of serious damage to hearing than any other currently available.

PART 4: STUDY OF COCHLEAR FUNCTION IN SMALL AS COMPARED TO LARGE FENESTRA STAPEDECTOMY

In order to evaluate the possibility that one fenestra size in stapedectomy might influence the rate of development of inner ear dysfunction more than another postoperatively, a separate study was carried out to measure changes in bone conduction thresholds in three subgroups of patients whose investigative data conformed to certain selected criteria, in order to evaluate the roles played by the disease process, overall effects of stapedectomy, and fenestra size in determining the future function of the cochlea.

Because their investigation data failed to conform to prearranged criteria, the following categories of patients were excluded from this assessment:

1. Those who had no registrable preoperative bone conduction (operated upon with a view to improving their use of amplification).

2. Those in whom tests of speech discrimination were not carried out at all phases of their evaluation, usually early patients attending peripheral hospitals lacking this facility.

3. Those having prior ipsilateral stapedectomy.

4. All those whose follow-up attendances were erratic. These were excluded to limit the problem of rogue sampling.[2]

5. All those suffering severe postoperative sensorineural loss (Part 3).

NATURAL HISTORY OF SENSORINEURAL HEARING LOSS IN UNOPERATED EARS

In order to determine the role of the

disease process in the outcome of stapedectomy, the hearing status of the contralateral ear in all patients undergoing *unilateral* operations was appraised to compare the rate of bone conduction deterioration in ears with no conductive loss at the first test with the rate of bone conduction deterioration in ears with conductive losses. Our aim was to evaluate the effect of otosclerosis on inner ear function and to determine what evidence there was from this study to support the proposition that perceptive hearing loss due to otosclerosis does not occur in the absence of stapes fixation.*

Both groups were tested for significant differences in response by a series of independent *t*-tests. Since all responses were measured relative to an arbitrary baseline of 30 dB, significantly different levels of response at subsequent follow-up would therefore be indicative of differing rates of hearing deterioration between these two groups. An attempt to control extraneous variation arising from hearing loss due solely to presbycusis was made by using the age-hearing response curves of Glorig and Davis[43] to estimate the probable age-based hearing loss at the various follow-up periods. This estimated loss was then added to each response score to produce hearing response values reflecting solely the conditions under study. In the absence of quoted aging curves for responses at 0.5 kHz and for percentage speech discrimination scores this correction was only possible for responses at 1, 2 and 4 kHz. In ears with conductive losses the bone conduction responses at each frequency were adjusted appropriately to eliminate the Carhart notch effect.

A series of 30 comparisons (comparison of responses at 0.5 - 4 kHz, and percentage speech discrimination scores at each of 1, 2, 3, 5, 7 and 10-year follow-up periods) was carried out. Of these, 17 differences were found to be significant at the 2.5% probability level or better (in all 17 cases the mean response for ears with no conductive loss was observed to be significantly better than the mean bone conduction for those with a conductive loss). Marked differences in the relative responses of the two groups were observed at the various test frequencies. At 0.5 kHz and 4 kHz highly significantly ($P < 0.01$ or better) superior performances in ears with no conductive loss were observed at all six follow-up periods. Again, at 1 kHz five of the observed differences in favor of this group were found to be statistically significant, one at the $P < 0.025$ level and the others at $P < 0.01$ level or better. However at 2 kHz and for percentage speech discrimination scores no significant differences were observed at any follow-up period. Our results therefore give clear evidence that the patients suffering from mixed hearing losses experience substantially more rapid hearing deterioration than those with no conductive hearing loss, and that this differential deterioration is frequency dependent, being most marked at the 0.5 kHz and 4 kHz ends of the frequency spectrum and effectively disappearing at 2 kHz.

DISCUSSION

The controversy as to whether sensorineural hearing loss can be caused by otosclerotic involvement of the cochlea has not yet been finally resolved. Although Glorig and Gallo[44] found no grounds for an association, our own findings and the weight of clinical evidence supports the belief that sensorineural loss is commonly greater in patients suffering from clinical otosclerosis.[45-49]

We propose that the sparing of the 2 kHz response in ears with mixed deafness has an anatomical basis. The upper basal turn which mediates this response is that part of the cochlea which lies furthest from the fissula ante fenestrum, the most frequent site of otosclerosis. Therefore it will be involved less often, later, and less extensively than other areas when the focus of abnormal bone enlarges.

We compared deterioration in bone conduction in nonoperated ears of patients having unilateral stapedectomy, in order to discover if there was any evidence of cochlear otosclerosis in ears without conduction hearing loss. Our investigation was based on the supposition that these ears were "at risk" because the pair of each had surgically proven otosclerosis.

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*Schuknecht HF: Personnal communication, 1973.

While Schuknecht and Gross[50] believe that otosclerosis probably but rarely aggravates normally occurring atropic changes in the cochlea, Schuknecht and Kirchner[51] emphasize that they have not encountered any histological evidence to support the view that isolated sensorineural loss can occur independent of conductive loss in otosclerosis. In other words, in their view, there is always concomitant footplate fixation.

Bosatra[52] reported that only 5% of temporal bones from otosclerotic patients had involvement of cochlear structures. If we assume that this incidence is correct for our particular population of patients, then we cannot expect that cochlear involvement has contributed much to the sum total of sensorineural impairment in the small number of ears in this study. Alternatively, if cochlear otosclerosis per se exerted any effect, this could have been both equal and cancelling in each group. Obviously further data from a control group of nonotosclerotic patients would be required in order to answer this question.

COMPARATIVE BONE CONDUCTION CHANGES IN OPERATED AND UNOPERATED EARS

In order to assess the risks to the cochlea from stapedectomy overall, the relative performance of operated and unoperated ears in otosclerotic patients was assessed using bone conduction responses at 0.5, 1, 2 and 4 kHz and percentage speech discrimination. No attempt was made to stratify the data by patient age. With the small numbers involved in this study, any further reduction in numbers would be self-defeating. In unoperated ears with conductive losses the responses at each frequency were adjusted appropriately to eliminate the Carhart notch effect.

As before, the number of patients with superior performance in the operated ear, and the number with superior performance in the unoperated ear were recorded for each follow-up period and for each response type. These figures were tested against the null hypothesis of no difference in relative rates of deterioration (which implies equal numbers of superior operated and unoperated ears) by a Chi-squared goodness of fit test. Detailed examination of the data relating to each response type showed that in three instances the numbers were equal, the number of superior operated ears exceeded the number of superior unoperated ears on 14 occasions, and superior unoperated ears exceeded superior operated ears on 8 occasions.

Of the 25 data sets tested, only 4 showed significantly different relative rates of deterioration, 1 suggesting superior performance in the unoperated ears and 3 suggesting superior performance in the operated ears. It must be borne in mind that when a large number of significant tests are carried out the occurrence of a small number of apparently significant results attributable solely to chance must be expected. In view of this and of the conflicting nature of those results which were significant we conclude:

1. These data offer no evidence of differing rates of hearing deterioration in operated and unoperated ears.
2. Stapedectomy, in terms of future cochlear function, is advantageous for those patients who are not in the "at risk" category previously discussed (Part 3).

SHORT AND LONG TERM EFFECTS ON COCHLEAR FUNCTION IN SMALL AS COMPARED TO LARGE FENESTRA STAPEDECTOMY

This investigation was performed to determine whether a relationship existed between fenestra size and postoperative cochlear dysfunction.

Retrospectively it was obvious that some of the cases of immediate severe sensorineural hearing loss described in Part 3 of this article were likely to be the result of physical trauma to the inner ear structures for which there was no known treatment. At the same time, functional depression, had it a vascular basis, might well have been treated successfully, provided the diagnosis came early.

In the hope of gaining some insight into the effects of stapedectomy on cochlear function, and with a view to initiating treatment when necessary, bone conduction thresholds were monitored in the operated ear at regular intervals postoperatively. It was already known that considerable initial depression of bone conduction thresholds occurred after fenestration of the lateral semicircular canal[53] and after fat wire stapedectomy.[54]

Our main concern was to measure the degree of dysfunction which occurred postoperatively and to discover to what extent it was either recoverable or progressive. This investigation had two parts: 1) preliminary: to compare the amounts of dysfunction with the size of the oval window fenestration in the first three months postoperatively in a small selected group of patients, 2) long-term: to evaluate the effect of fenestra size on the 0.5, 1, 2 and 4 kHz responses from one year onwards in the series as a whole.

As previously indicated, the operations were classified categorically:

1. Small fenestra stapedectomy (SFS); the diameter of the footplate fenestration was 0.4 mm or less.
2. Large fenestra stapedectomy (LFS); the diameter of the footplate fenestration was greater than 0.4 mm, half or more of the footplate being removed.

Preliminary Study. All patients had bone conduction tests (0.5 - 4 kHz) carried out on the day prior to operation, on the first five postoperative days (at approximately the same time each day) and then at one month and three months. Testing was performed in a sound-proof booth using standard masking technique.

With a view to estimating a possible relationship between preoperative function, the fenestra size and alterations in bone conduction thresholds, all the pa-

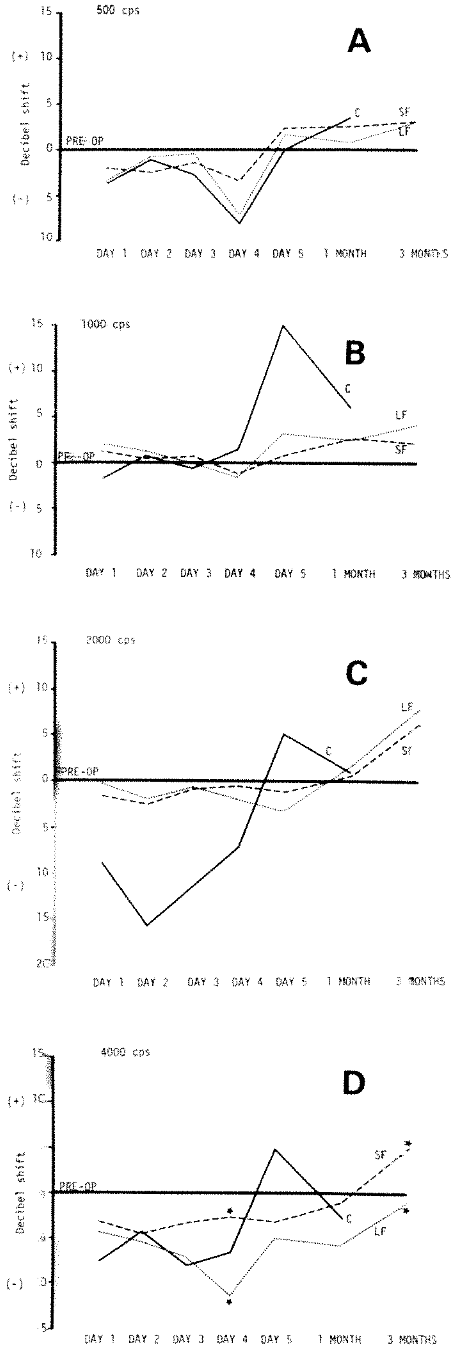

Fig. 3. Postoperative bone conduction responses at A) 500, B) 1000, C) 2000, and D) 4000 cps at intervals after small fenestra stapedectomy (SF), large fenestra stapedectomy (LF) and myringoplasty controls (C). *Significant differences.

tients were allocated to Shambaugh groups.[3] The early cases in the series were operated on using either 0.8 mm Teflon® and Teflon® wire pistons or Gelfoam® wire prostheses. Consequently, these were in the "large" category (LFS). In the later patients, whenever possible, a central fenestration of about 0.4 mm in diameter was made and an 0.3 mm Teflon® piston used (SFS). Ears with an intact ossicular chain in whom a simple perforation was repaired using an underlaid fascial technique, were used as controls. Seventy-two SFS and 54 LFS and 16 control ears were investigated.

Results. The mean postoperative change in bone conduction threshold for each of the stapedectomy operations and also the control group through the four speech frequencies, are represented graphically in Figures 3-6. Overall these demonstrate an immediate depression of bone conduction which gradually lessens during the first one-month period. On the whole, the effect is greater for LFS than SFS, but where differences exist, these are only significant for 4 kHz at the fourth day and third months postoperatively. The changes of response in the control ears suggest that some of the effect in stapedectomized ears can be attributed to alterations in the physical character of the ear canal and mesotympanum by blood clot and dressing (through the transmission component in bone conduction testing).

The considerable improvement in the bone conduction response of the control ears at 500 cps may be due to a temporary enhancement of the natural vibratory characteristics of the middle ear consequent on its altered physical state.

In order to discover whether prognostic information could be gained from the results of this investigation, the statistics were looked at in a number of ways. It was decided that changes of less than 10 dB were probably not meaningful. Two of the analyses provided significant differences between SFS and LFS.

1. The number of ears showing a bone conduction loss of 10 dB or more at *any* frequency at one month were compared with those meeting the same criterion at three months. With SFS an incidence of this finding in 21 out of 72 ears at one month fell to 13 out of 72 at three months. With LFS the incidence was virtually the same at one and three months (13 out of 54 and 12 out of 54). This suggests that when this finding is present at one month, there is a much greater chance of full recovery in SFS ears than in LFS ears.

2. The numbers of ears showing a depression in bone conduction of 10 dB or more in any two frequencies in the first four postoperative days were compared with those meeting the same criterion at the three-month test (final result).

A. The early and final results for all ears (SFS and LFS together) were compared. Twenty-five ears which were failures early (bone conduction depressed by 10 dB or more at two frequencies in the first four postoperative days) were eventually successes (less than two or no frequencies depressed by 10 dB at the three-month test). Whereas of the 86 early successes, only two eventually became failures. In other words, of the early failures, 19.35% remained failures, whereas among the initially successful, only 2.33% became eventual failures. (The difference between these results is a significant one, $P < 0.01$.) Thus from a prognostic point of view, the bone conduction responses in the early stages give a useful indication of the chances of a successful outcome — when there is an early failure, then there is a 5 in 1 chance that this will persist and when the early result is favorable there is only a 1 in 50 chance that this will not be maintained.

B. The SFS ears were analyzed separately in the same way. Although the majority of the final failures came from the early failure group, the differences between the two groups were not significant. Thus it appears that in SFS the final outcome is not influenced by the early postoperative course.

C. The LFS ears were analyzed separately as in Group A. As in the combined analysis it was found that the risks of a final failure were significantly greater in ears where there was an early failure.

D. Finally the failure rates with SFS and LFS were compared and were found to differ by almost 6%. Although this is not a significant difference ($X^2 = 0.73$), it may become so with the accumulation of more data.

Conclusions.

1. An early depression of bone conduction threshold suggests a bad prognosis for the three-month test.

2. Although in comparing SFS and LFS the overall differences in bone conduction change at all frequencies are not significant, the possibility that they may become so when new evidence is added to the current statistics, is suggested by

3. The significant difference between the effect of SFS and LFS on the 4 kHz response. That this is the frequency most susceptible to the effects of trauma, toxins and aging, argues for the contention that the smaller the fenestra, the greater the safety of the cochlea.

Long Term Study. This was conducted subsequently as a completely separate assessment of changes in bone conduction thresholds in the series as a whole over a much longer period. Its purpose was to discover whether the findings in our preliminary study would be borne out in a larger group followed-up for much longer periods.

Changes in bone conduction thresholds (0.5 - 4 kHz) and speech discrimination scores at intervals of 1, 2, 3, 5, 7, 10 and 15 years postoperatively were documented on separate work sheets which also recorded a number of other parameters which might influence the outcome. These included age in decades, the fenestra size, the footplate pathology, the prosthesis type, the Shambaugh group, and the occurrence of any previous stapes operation. In order to assess the role of trauma, operative problems considered likely to damage the cochlea were recorded. In order to provide a more objective assessment of the incidence of trauma, the duration of the operation and the length of hospital stay were also recorded on each work sheet. In order to compare the rates of development of bone conduction loss in operated and nonoperated ears, changes in bone conduction in all contralateral nonoperated ears were recorded. This information was then transferred to cards and analyzed by the ICL 1906S computer.

Results. The analysis of the data on the 655 ears in this exclusive group was as follows:

GENERAL PROFILE.

1. Age: 72% were aged less than 50 years.
2. Fenestra size: 25% were small fenestra operations.
3. Footplate pathology: Rim otosclerosis was recorded in 64%, biscuit footplate in 28% and obliterative otosclerosis in 8%.
4. Prosthesis type: Polyethylene strut 9% standard (0.8 mm diameter) Teflon® piston 26%, Teflon® wire (0.8 mm diameter) piston 22%. Gelfoam® and wire prosthesis 16%, very slim shaft (0.3 mm diameter) Teflon® piston 24%.
5. Shambaugh Group: 56% were Group A, 34% Group B and 10% were Group C.
6. Previous stapes mobilization had been performed in 5%.

SURGICAL TRAUMA.

1. Surgical notes indicated "traumatic events" during the operation in 25%. These were excessive loss of perilymph in 11%, fenestration of the footplate by drilling in 5%, difficulty with inserting the prosthesis in 4%, early excessive mobility of the footplate (floater) in 3.2% and the entry of blood into the vestibule in 2%.

TABLE 17. COMPARISON OF SMALL AND LARGE FENESTRA STAPEDECTOMY CORRECTED FOR EFFECTS OF AGE AND SHAMBAUGH GROUPING

Length of Follow-up (yr)	*Response*				
	0.5 kHz	*1 kHz*	*2 kHz*	*4 kHz*	*Percentage Discrimination*
1	NS*	$P < 0.001$*	$P < 0.01$*	$P < 0.05$**	$P < 0.001$**
2	NS*	$P < 0.001$*	$P < 0.001$*	NS**	$P < 0.05$**
3	NS*	$P < 0.05$*	$P < 0.05$*	$P < 0.001$**	NS**
5	NS**	NS*	$P < 0.05$*	$P < 0.05$**	NS**
7	NS**	NS*	NS*	$P < 0.05$**	$P < 0.01$**
10	NS**	NS*	NS**	NS**	NS*

*Superior response from LFS.
**Superior response from SFS.
P - Probability of observed differences in responses occurring by chance.
NS - Observed differences not statistically significant.

2. Forty-six percent of the operations were performed in less than 30 minutes. Only 2% lasted more than one hour. The duration of hospital admission was "normal" (five nights or less) for 97% of patients.

LONG-TERM CHANGES IN BONE CONDUCTION. A comparison of changes in the bone conduction response and speech discrimination with SFS and LFS, corrected for the effects of age and Shambaugh grouping by the technique of orthogonalized analysis of variance, are set out in Table 17. It can be seen that SFS caused significantly less depression of bone conduction thresholds with the passage of time at 4 kHz. This effect was conspicuously absent at 0.5 kHz and was reversed at 1 and 2 kHz. Better speech discrimination scores were achieved with SFS in all but one postoperative evaluation.

DISCUSSION

Although the exclusion of those patients with no registrable preoperative bone conduction has introduced bias in regard to age distribution, the general profile of this series is similar to that of most others which have been reported in detail.

Surgical Trauma. Although "traumatic events" are recorded as occurring once in every four operations, we believe they can be disregarded because they do not appear to have affected the eventual bone conduction levels in any identifiable way. This decision is supported by, 1) the negligible number of patients whose immediate postoperative course was complicated by either excessive vertigo or severe depression of bone conduction thresholds sufficient to prolong their hospital stay, and 2) the small number of operations whose duration was excessively long (greater than one hour).

Deterioration in Bone Conduction Thresholds. The results of this investigation show clearly that sensorineural hearing loss can complicate any type of stapedectomy. It is concluded that the risks of immediate and delayed overall loss (Part 3) and of delayed progressive high tone loss are related principally to the fenestra size, a belief supported by a relationship between the degree of inner ear damage and the size of labyrinthine fistula complicating mastoid surgery[55] and cholesteatomatous middle ear disease.[56]

In our view, SFS is an important advance in the surgical treatment of otosclerosis but it must not be forgotten that although it significantly lessens the loss of high tone response with time, it certainly does not eliminate the problem. In addition, it should be noted that SFS did not provide better bone conduction at 0.5 kHz and provided less satisfactory thresholds at 1 and 2 kHz than did LFS.

In order to explain the lack of uniformity in these results, we have to consider the possible ways in which one operation might influence bone conduction more than the other, under the following headings:

1. Energy transmission to the cochlea.
2. Effects on the sensory apparatus.

ENERGY TRANSMISSION TO THE COCHLEA. The response of the cochlea to bone conduction stimuli has three components, all of which may be influenced by the size of the oval window fenestration.

1. The contribution of translatory and especially transmitted factors in bone conduction are directly related to the overall efficiency of the ossicular chain. In LFS a mesothelial membrane develops on the vestibular aspect of the prosthesis and forms a tent anchored at the fenestral rim having its apex at the prosthesis.* This system works first, by producing a good fluid-tight seal in the vestibule proper and, second, because the membrane, owing to its diameter being greater than that of a piston has less impedance. The acoustic impedance (Z_a) in the plane of the piston is the ratio of the mechanical impedance (Z_m) and the square of the area of the acting surface of the piston: $Z_a = \frac{Z_m}{S^2}$.[57] This transmission system being less rigid than the footplate entails some losses. Nevertheless, it is more efficient than one would obtain with a very narrow piston projecting through a very narrow opening and giving rise to a much smaller membrane than that occurring in LFS.** Therefore better overall hearing should be provided by LFS if only by virtue of its being a better mechanical system than SFS. Although this effect may account for the significantly better bone conduction response at 1 and 2 kHz, the lack of better response with LFS at 0.5 kHz presents a problem. It is proposed that a better match between the surface area of the oval window membrane and the diameter of the scala vestibuli is provided by LFS as compared to SFS. Consequently in theory, LFS would deliver more energy to the low frequency receptors at the furthest end of the cochlear duct. The explanation as to why this is not apparent in practice may be that the impedance of the cochlea which is much greater for the lower frequencies masks the differences in the respective responses with LFS and SFS in such a way as to render them too small to show significance. Again, cochlear impedance may override the theoretical advantage arising from removal of the rigid footplate, which would be expected to reduce middle ear impedance for low frequencies.**

2. Compressional bone conduction depends upon differential mobility of the oval and round windows. Footplate fixation is responsible for an impairment of bone conduction response which is maximum for 2 kHz. Stapedectomy will provide a much better restoration of compressional bone conduction when most or all of the footplate is removed. One would not expect a fenestra of 0.4 mm to do much to reverse a Carhart notch. Herein appears to be at least part of the explanation for significantly better bone conduction thresholds at 1 and 2 kHz with LFS.

EFFECTS ON THE SENSORY APPARATUS. In spite of its undoubted mechanical deficiencies, SFS provides a significantly better bone conduction response at 4 kHz. This may be because SFS causes less trauma to the higher frequency receptors, which are already so vulnerable to high intensity noise, tobacco and aging. If an explanation for this can be found, it will be based on a better understanding of the events which occur in the labyrinth at and shortly following oval window fenestration and the changes which subsequently develop in the components of the cochlea as a consequence of those earlier events.

The problem basically concerns the multiplicity of possible responses to trauma. In tissues generally, there would appear to be an inverse relationship between cell complexity and reparative potential. Therefore, in an organ as highly specialized as the cochlea, we could expect a less complete recovery than we might after a simple skin incision. Every organ has its own specific ability to survive trauma; however, once the upper limits of tolerance have been passed, the outcome will depend upon:

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*Schuknecht HF: Personal communication, 1977.

**Tonndorf J: Personal communication, 1977.

1. The specific potential of that organ tissue for repair. Reports on experimental stapedectomy have recorded outer hair cell loss postoperatively.[58] It has been postulated that some of the high frequency losses which follow stapedectomy may be the result of surgically induced stimulation injury.[59] Similar lesions possibly account for some or all of the hearing losses in this series. The inability of hair cells to regenerate (fixed postmitotic state) is an example of the special vulnerability of the cochlea to trauma.

2. The functional reserve of the organ. In the cochlea this factor is important and most valuable, as illustrated by the maintenance of bone conduction thresholds in the face of a loss of up to 75% of the first order neurones.[50]

3. The ability of the organism *as a whole* to compensate for functional loss. It is frequently possible to demonstrate subclinical defects in vestibular function by caloric testing after stapedectomy.[19,61,62]

Although the response of the ear to stapedectomy is as yet poorly understood, studies of long-term effects of diseases of the otic capsule on labyrinthine function strongly suggest that progressive accumulative degenerative processes may be initiated whose clinical manifestations may be delayed possibly for long periods.* In order to find an explanation for delayed sensorineural loss following stapedectomy, we can extrapolate from what we know about another type of delayed loss due to trauma, i.e., noise deafness, and postulate a theory which takes into account the mechanical aspects of the problem. Although the modes of action in these two mechanisms may not be identical, i.e., overstimulation as compared to membrane distortion, they could have a common denominator such as vascular sludging and spasm occurring as a basic response to trauma. The general principle that trauma causes vasospasm which if prolonged leads to thrombosis, is in line with the findings of Lawrence et al[63] and Schnieder[41] which suggest that the damaging effect of high intensity noise has a vascular and simultaneous biochemical and humoral basis.

Noise Exposure Data. At present much of our knowledge about the effects of excess energy on the cochlea is based on noise exposure experiments. It has been shown experimentally that exposure to high levels of noise results in:

1. Distortion of hair cells and swelling of their nuclei.[64]
2. Degenerative changes within the hair cell cytoplasm, with eventual membrane rupture and lysis.[65,66]
3. Reduction of ribonucleic acid,[67] endolymphatic oxygen tension,[68] and succinic dehydrogenase[69] and glycogen levels.[70]

It is tempting to reason that hair cell damage in the experimental animal is due to vascular changes and that these may be similar to those vascular changes observed in the human inner ear and interpreted as being part of the aging process.[24] If abnormal energy input, in this case loud prolonged noise which can occur during stapedectomy, can cause irreparable damage by virtue of exceeding the reserve capacity of the cochlea, then it may be possible that other forms of energy, in excess, regardless of their nature, could be traumatic also.

Mechanical Aspects. That a sudden loss of perilymphatic pressure occurs at the moment of footplate fenestration is indicated by the flow of perilymph which quickly fills the oval window niche in many stapedectomies. The immediate distortion of the membranous labyrinth which would appear to be inevitable, can be expected to affect ionic transport and microcirculation and the overall problem will be aggravated by the release of histamine.[41]

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*Schuknecht HF: Personal communication, 1977.

If stapedectomy can cause vasospasm and metabolic disturbance because of its hydraulic effect, the outcome must be related to the *size* of the fenestra which in turn determines the volume and rate of perilymph loss. It is to be expected therefore, that LFS would be more traumatic than SFS.

It is argued therefore that considerable hydraulic effects on the labyrinth must follow decompression of the perilymphatic space causing membrane distortion and an effect on the cochlea similar to that produced by excessive noise exposure. When structural loss occurs from both or either cause, this is the end result of primary vasospasm. If the effect of the progressive phases of vascular disease which have been attributed to aging[24] is similar to the degenerative process which follows trauma, then the clinical picture will resemble presbycusis but will be related more to the postoperative interval than specifically to years. Attempts to explain the particular susceptibility of the basal turn to delayed degenerative changes have been based on mechanical,[71,72] vascular[72] and enzymatic theories.[73] Possibly all these factors, together with a poverty of reserve due to other disease, including genetic defects, play a part in the development of this serious complication of stapedectomy.

CONCLUSIONS

The evidence from this part of our investigation supports the following:

1. Although cochlear involvement by otosclerosis may occur, we have no evidence that it causes sensorineural loss in the absence of footplate fixation.

2. There is no indication that the cochleas of ears undergoing uncomplicated stapedectomy suffer undue *generalized* degenerative changes as a direct result of operation (provided a clearly defined at risk group is excluded). The finding that generalized degenerative changes do not appear to advance more rapidly in the operated ear argues strongly in favor of stapedectomy as a better treatment than amplification through the use of a hearing aid in the younger patient with good cochlear function.

3. The size of the fenestra should be limited to the least possible in each operation in order to minimize the inevitable loss of high tone response which complicates all types of stapedectomy and which is very significantly greater following total removal of the footplate.

FINAL CONCLUSIONS

Throughout the world at the present time, practically all stapedectomy is of the large fenestra type. Its advantages are obvious, namely, that it is easier technically and provides a good overall early result in most instances. Its disadvantages are not so often apparent because difficulties in obtaining accurate and comprehensive follow-up information may lead to a lack of real awareness of the frighteningly high incidence of serious sensorineural loss occurring in the early postoperative period. Additionally, because there have been few studies of sufficient duration to reveal the long-term effects on high tone cochlear response and speech discrimination, the eventual effects on the patient's auditory capacity are not widely recognized.

It is clear that SFS with the 0.3 mm Teflon® piston has not been the panacea for all of our otosclerotic patients, largely because of mechanical inefficiency for the lower frequencies and a tendency to disarticulation from the incus due to faults in the characteristics of the loop of this prosthesis. It is hoped that a recently designed 0.3 mm Teflon® piston with a platinum loop will solve this problem. In all other respects, this technique does have an enormous advantage to recommend it. This is that the risk of immediate or delayed inner ear complications is significantly reduced. In addition, and most importantly, balanced frequency response is preserved and with it speech discrimination for assistance by amplification, if this is eventually required. For these reasons we contend that SFS is the best currently available surgical treatment for otosclerosis.

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15.1.79

DEVIATED NASAL SEPTUM

INCIDENCE AND ETIOLOGY

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SUMMARY — Septal deformity is of two kinds, which may occur independently, or together: 1) anterior cartilage deformity of the quadrilateral septal cartilage, caused by direct trauma or pressure at any age; and 2) combined septal deformity, involving all the septal components, caused by compression across the maxilla from pressures occurring during pregnancy or parturition. This is part of a facial deformity. The incidence of septal deformity was investigated in 2,380 Caucasian infants at birth, 2,112 adult skulls of five ethnic groups (European, Indian [Asian], Chinese, African and Australian Aboriginal), 918 mammals (266 higher and lower apes, 457 other placental mammals and 185 marsupials). The method of nasal testing of infants by passage of special testing struts (6 by 2 mm) is described. Forty-two percent of septa of infants were straight, 27% deviated and 31% kinked. A similar pattern was found in adult skulls, namely 21% straight, 37% deviated and 42% kinked. Anterior cartilage deformity occurred in about 4% of births. The maxillary molding theory of transmitted pressures during pregnancy or parturition, causing septal deformity, is described. The findings show that varying degrees of septal deformity occur at a constant rate at birth and in the adult. These may vary slightly for each ethnic type. Birth molding pressures are a major cause of dental malocclusion. The shape and strength of the skull and the erect posture appear to be major factors, for septal deformity did not occur in the lower animals, but occurred in 37% of the higher apes and also in a skull of a hominid 1,750,000 years old. This concept enables easy recognition at birth, and the carrying out of a rational method of treatment by manipulation and rapid maxillary expansion.

Only a few reviews of septal abnormalities in moderate numbers of skulls have been reported. Mackenzie[1] reported that in 2,152 adult skulls of varied races, 23% were straight, 67% were kinked (58% to the left), and 10% deviated; and Post[2] reported a survey of 2,353 skulls from 22 different races.

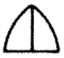
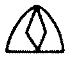
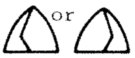
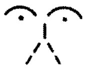
This paper reports the results of investigation of 2,380 Caucasian infants at birth, 2,112 adult skulls of five ethnic types (European, Indian [Asian], Chinese, African and primitive Australian Aboriginal), and 918 mammals comprising 216 higher apes (gorilla, chimpanzee), 60 lower apes (baboon, mandrill), 457 other placental mammals, and 185 marsupials. The findings showed that septal deformity in lower mammals was a rarity, but was present in 37% of the higher apes, the hominid *Australopithecus boiseii*, and, to a varying degree in humans, depending on the race (most likely related to shape and strength of the skull and also to the assumption of the erect posture). These findings are then correlated with the maxillary molding theory[3-5] of the etiology of septal deformity.

There are two basic kinds of septal deformity which may occur independently, or together; namely anterior cartilage deviation and combined septal deformity.

ANTERIOR CARTILAGE DEVIATION

This bend or buckle, localized to the anterior quadrilateral cartilage, is frequently associated with asymmetry of the external bony pyramid and dislocation of the cartilage off the anterior nasal spine. In this investigation of 2,380 Caucasian babies (Table 1) it was found to occur in about 4% of normal vaginal deliveries, increased in cases of severe pressure such as persistent occipitoposterior positions (13%) but rarely in cases of caesarian section. These findings are similar to other reports.[6,7] The deformation mainly occurs during internal rotation,[5] because of some extension of the head from pressure on the side of the jaw by the oncoming shoulder, which causes the side of the

TABLE 1. INCIDENCE OF SEPTAL DEFORMITIES IN BIRTHS (N = 2380)

TYPE	NO.	STRAIGHT 	BILATERAL 	UNILATERAL 	EXTERNAL 
S.V.D.	2094	43%	26%	31%	79 in 2094 4%
ELECTIVE L.U.C.S.	106	48%	25%	27%	NIL
NON-ELECTIVE L.U.C.S.	113	40%	34%	26%	NIL
P.O.P.	67	26%	37%	37%	9 in 67 13%
TOTAL	2380	42%	27%	31%	4%

△ Straight septum. △ Septal deviation or bilateral deformity. △ Septal kink or spur to right (deformity assessed as if looking at the baby). △ Septal kink or spur to left. S.V.D. - Spontaneous vaginal delivery. L.U.C.S. - Lower uterine caesarian section. P.O.P. - Persistent occipitoposterior position.

forehead and nose to be wiped across the wall of the pelvis. This deforms the nasal cartilage and also may cause depressed fracture and distortion of the bony pyramid. The method of production has been well-described by Jeppesen and Windfield.[6] This deformity comprises in a varying degree:

1. External deformity, with asymmetry of the external nares and bending of the anterior septal cartilage and columella (Fig. 1).

2. Distortion and depressed fracture of the bones of the nasal pyramid (Figs. 2, 3).

3. Distortion of the junction of the septal cartilage and maxillary spine (Fig. 3).

4. Angulation deformity of the jaw[5] (Fig. 4).

This deformity usually reduces itself, but if still present three days after birth, I consider that distortion of the nasal bones and dislocation of the cartilage on the maxillary spine are still present, and manipulation should be done. The angulation deformity of the jaw, which occurs in about 10% of cases, usually disappears by the age of six months.

In the review of 2,112 adult skulls (Table 2), a close association of distortion of the bony nasal pyramid with anterior cartilage deformity was found. Figures 5 and 6 are typical examples. Figure 7 shows considerable cartilage deformity in a child aged four years with no history of direct trauma. These findings are consistent with previous anterior cartilage deformities, but they may occur at any age from direct trauma.

COMBINED SEPTAL DEFORMITY

All the septal components are involved,[4,5] namely the vomer bone, the perpendicular plate of the ethmoid bone, and the quadrilateral cartilage. There may be a kinking or spur deformity at the vomer-ethmoid junction,

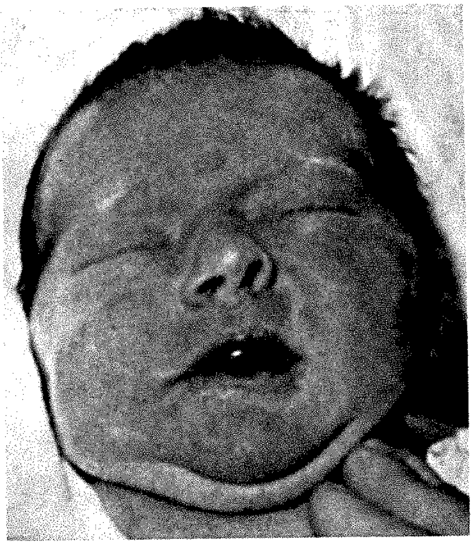


Fig. 1. Three-day-old baby showing external deformity of the nose and columella, and asymmetry of the external nares.

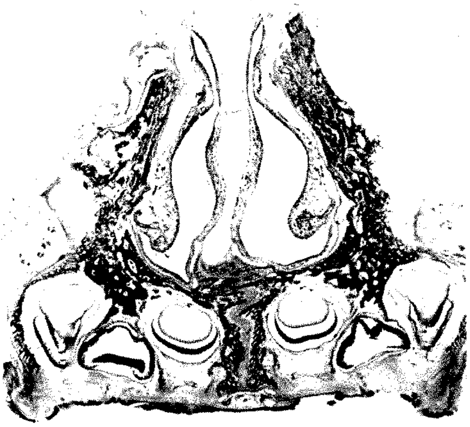


Fig. 3. Section at birth of anterior end of maxilla viewed from the front. Note dislocation of the cartilage to the right of the maxillary spine, and depressed deformation high up of the left nasal bone. There is also elevation of the floor of the nasal fossa on the left which is associated with a combined septal deformity.

or "C" or "S" shaped bending or deviation, or a combination of them. There are always associated abnormalities, such as irregular hypertrophy of the lateral walls of the nose, on the side of the concavity of the septal deformity, as postulated by Proetz.[5] There are also usually deformities of the cheek, the external nares, the nasal fossae, and the palate, and malocclusion of the teeth. Thus it is a facial deformity, of which the septal deformity is a part. Figure 8, an Indian (Asian) skull, demonstrates well the kink deformity of the septum, the elevation of the nasal fossa on the side opposite to the kinking, and the characteristic compression and distortion of alignment of the teeth of the maxilla on the same side as the palatal elevation. Figure 9 is the skull of a

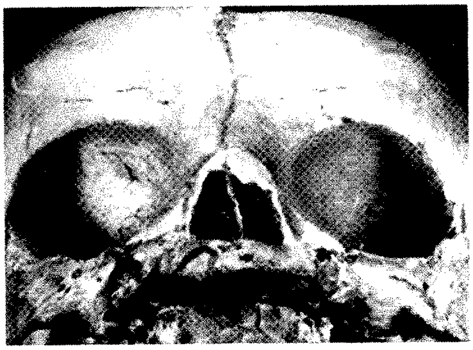


Fig. 2. Infant skull showing depressed fracture of the nasal bones at birth. Note depression of the left nasal bone, and deformation on the right with anterior cartilage deformity. There is also parietal bone molding. (Reproduced from Steiner A: Md State Med J 8:557, 1959, by permission of the author).

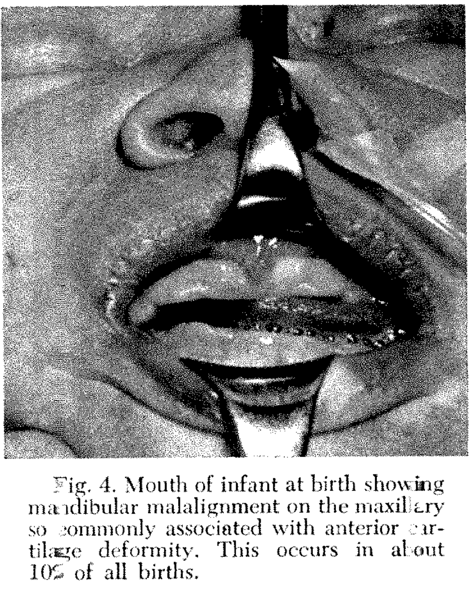


Fig. 4. Mouth of infant at birth showing mandibular malalignment on the maxillary so commonly associated with anterior cartilage deformity. This occurs in about 10% of all births.

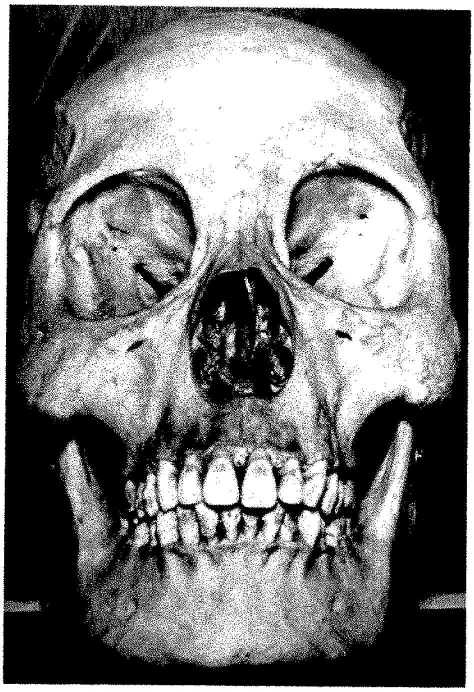


Fig. 5. Adult skull showing deformed bony external nares with anterior cartilage deformity.

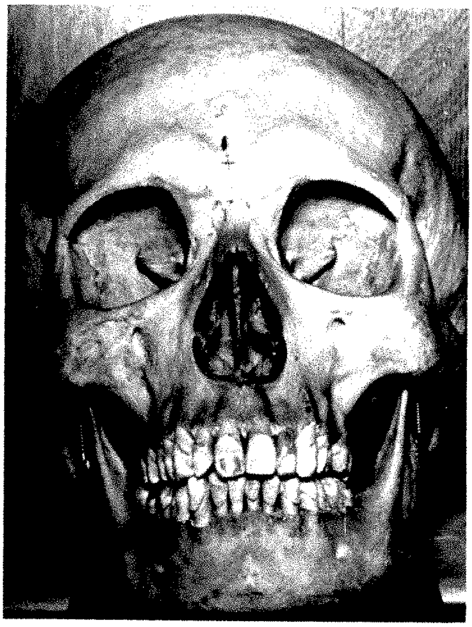


Fig. 6. Adult skull showing no bony external nares deformity and straight anterior cartilage. Note the elevation of the floor of the right nasal fossa which was associated with combined septal deformity and septal spur to left posteriorly.

primitive Australian Aboriginal demonstrating the elevation of the floor of the right nasal fossa with tilting of the maxillary spine with its groove to the left, the compensatory hypertrophy of the right inferior turbinate on the concave side of the septal spur (which is to the left), and the maxillary compression on the right causing a partial crossbite on that side.

The upper teeth normally articulate with the lower teeth so that the lateral edge just overrides, or is just lateral to, the lower teeth. Crossbite is present when the upper teeth are in line with, or medial to, the lateral edge of the lower teeth. The mandible may swing to one side to improve the alignment of the cusps of the teeth, thus aggravating

TABLE 2. PERCENTAGES OF COMBINED SEPTAL DEFORMITY IN ADULT SKULLS (N = 2112)

Race	*No. of Skulls*	*Straight %*	*Deviated %*	*Kinked %*
Indian (Asian)	269	13	38	49
Chinese	212	15	40	45
European	395	17	34	49
African	227	20	30	50
Australian Aboriginal	1009	27	38	35
Combined result	2112	21	37	42

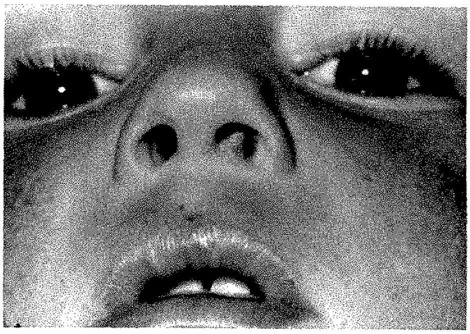


Fig. 7. Child aged 4 years demonstrating buckle of quadrilateral cartilage.

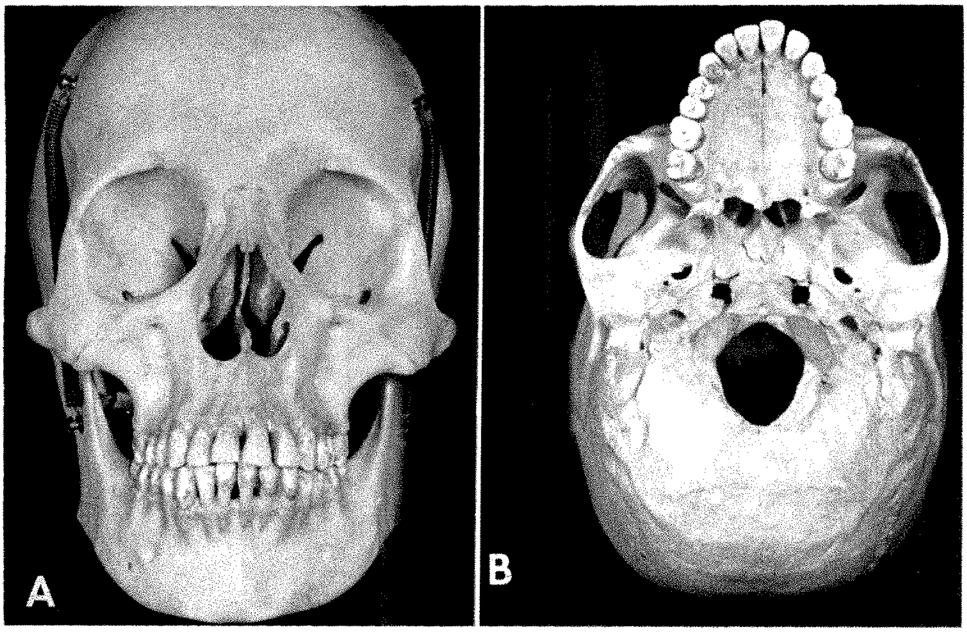


Fig. 8. Indian (Asian) skull. A) Note kink deformity of the septum to the right, elevation of floor of nasal fossa on the left, and mandibular swing from the midline. B) Note the distortion of alignment of teeth on the left side of the maxilla, compared with the even curve on the right.

the crossbite. Compression of the maxilla is a major cause of crossbite, and crossbite usually signifies underlying maxillary compression with its associated septal and facial deformity. Indeed, the type of septal deformity can be predicted with a high degree of accuracy by observing the dental malocclusion, and similarly, the dental condition by the inspection of the nose.[9]

RESULTS

CONSIDERING THE INVESTIGATION OF BABIES

As assessment of the septal configuration in infants is extremely difficult by anterior rhinoscopy; a new method of testing the nasal patency and septal deformity by the passage of polyethylene struts, 6 mm wide by 2 mm thick, has been used[5] (Fig. 10). (The external nares grows in vertical dimension from

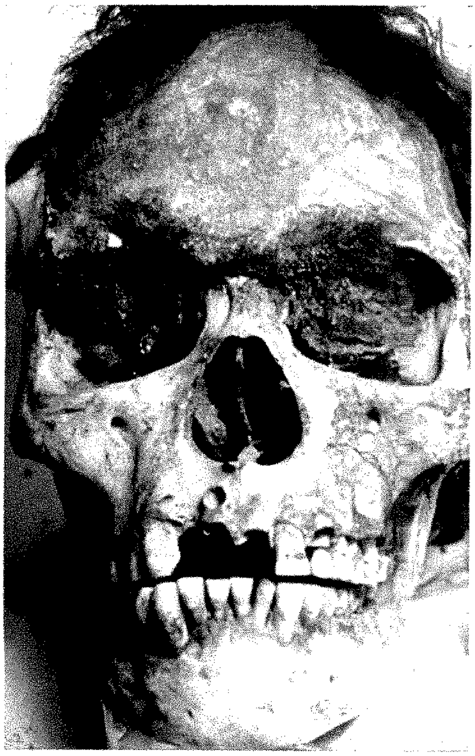


Fig. 9. Primitive Aboriginal skull. Note the elevation of floor of right nasal fossa, tilting of vomer and kinking of septum to left, the hypertrophy of the right inferior turbinates, and the tendency to crossbite.

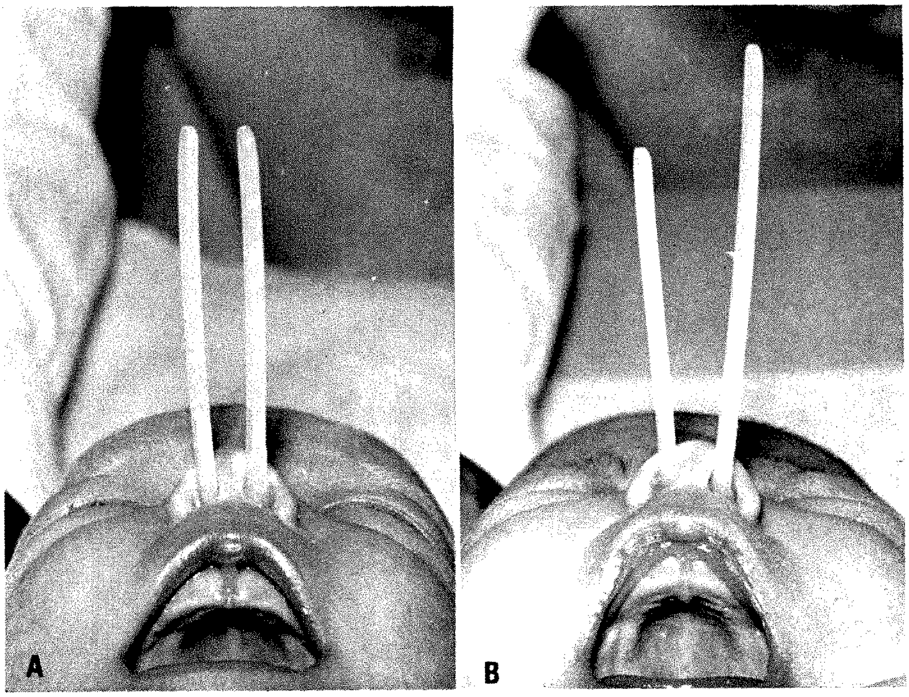


Fig. 10. Nasal testing procedure. A) Note the even passage of struts (6 by 2 mm) on the left with normal straight septum. B) On the right there is obstruction to the passage of the strut down the baby's left nose and normal passage on its right.

6 mm at birth to 12 mm in the first year.[8])

The lubricated strut is inserted upward 3 to 4 mm to get into the nose, then slid along the floor of the nose, hugging the septum. To do this, the outer end of the strut must be pushed toward the top of the head, temporarily deforming the external nares. The feeling of normal smoothness (i.e., a straight septum), some irregularity or roughness, or frank obstruction (i.e., septal deformity) is readily appreciated. The strut must be inserted very gently along the floor of the nose; it must not be pushed hard. It may pass through the posterior choanae but the frank obstruction occurs about 1.5 to 2 cm from the nares.

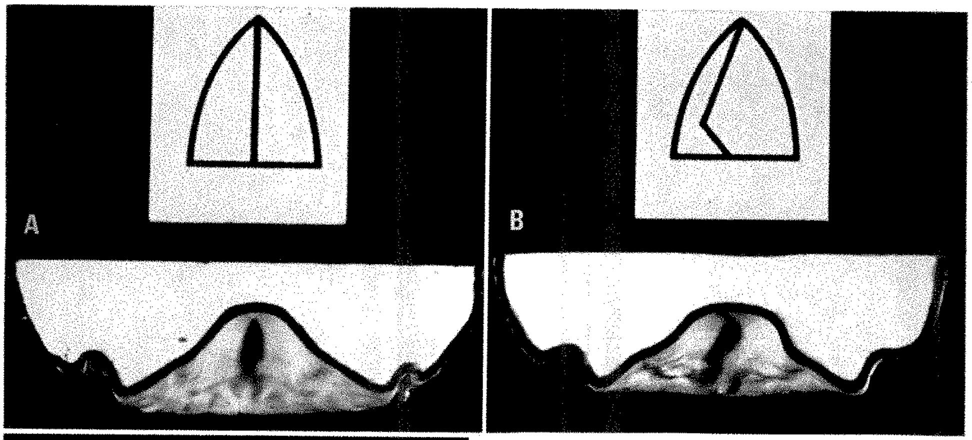
Table 1 gives the results of six months of normal routine testing of 2,380 Caucasian babies which is now done by the senior nursing staff of the King Edward Memorial Hospital for Women. These results are similar to those previously

TABLE 3. PERCENTAGE OF SEPTAL KINKING TO LEFT

Race	%
European	51
Indian	65
Chinese	56
African	54
Australian Aboriginal	59
Babies	55

TABLE 4. PERCENTAGE OF UNEVENNESS OF EXTERNAL NARES IN SKULLS (N = 2112)

Race	*Total* %	*Elevated on Right*	*Straight Septum*
Indian	33	50	NIL
Chinese	33	52	NIL
European	37	42	NIL
African	20	50	NIL
Australian Aboriginal	32	54	NIL



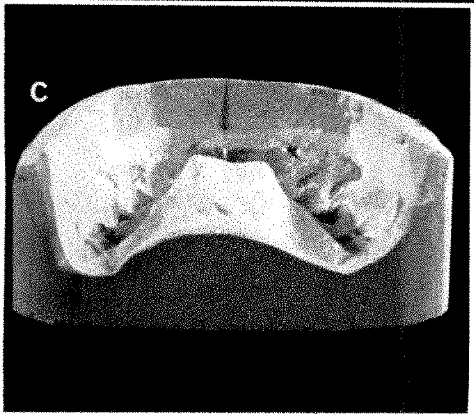


Fig. 11. Palatal changes. A, B) Coronal sections of casts of the maxilla at birth showing in A an even symmetrical palate with a straight septum (strut tested) and in B, asymmetry of the palate, compressed on the left, with septal kinking to the right (strut tested). C) Elevation of the left side of the dome, steepness and narrowing of the left side of the palate in a child aged 3½ years with a septal kinking to the right present since birth.

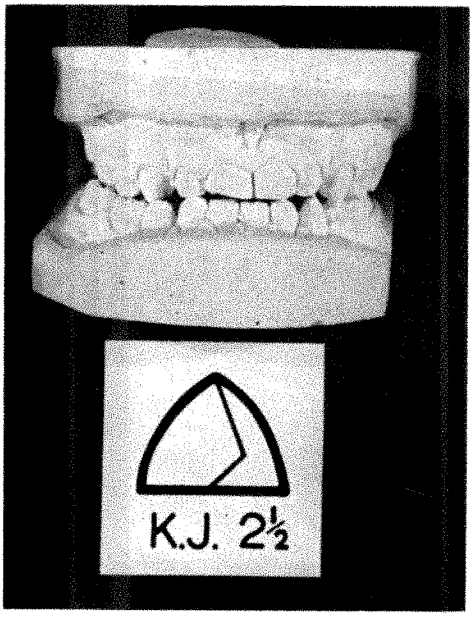


Fig. 12. Dental cast of child aged 2½ years with septal kinking to the left (present since birth). Note the crossbite of all the molar teeth on the right and mandibular swing from the midline. The palate was narrowed and elevated to the right.

reported by Gray, 815 in 1965[3] and 2,000 in 1974.[5]

CONSIDERING COMBINED SEPTAL DEFORMITY

Table 1 demonstrates the decreasing incidence of straight septa with increasing parturition pressures, namely elective lower uterine caesarian section (LUCS), 48%; spontaneous vaginal delivery (SVD), 43%; nonelective LUCS, 40%; and persistent occipitoposterior (POP), 26%. Elective LUCS has the least pressure, for the operation is performed before labor commences. Spontaneous vaginal delivery can be considered as normal average pressure during parturition. In nonelective LUCS, or trial of labor, considerable pressure has occurred with partial descent of the fetus, and so one would expect the results to be similar to or worse than SVD. In the abnormal posture of POP, bigger cranial diameters than in SVD are pre-

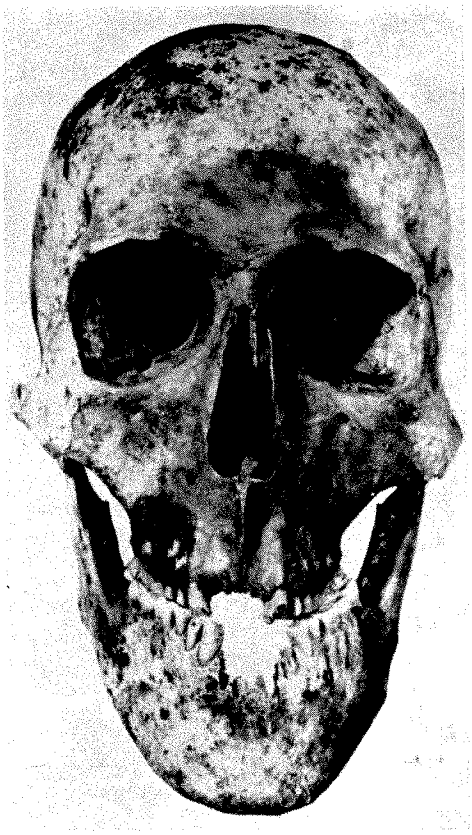


Fig. 13. Ancient Egyptian skull. Note the elevation of floor of right nasal fossa and tilting of vomer bone to the opposite side. Reproduced from *Digging Up Bones* (Plate 4C) by kind permission of the author D. R. Brothwell and trustees of the British Museum (Natural History).

sented, inevitably increasing the pressures on the skull. A higher incidence of unilateral kinking than deviations occurred in all the series. Review of many of these cases after several years has shown a similar deformity still to be present. Over 80% of straight septa were still straight, and some 95% of deviations were still present when 75 were reviewed in 1967.[10] Deformities in a few cases have been followed up by dental casts.[4] In babies with snuffles it has been found that septal deformity is usually present, acting as a big contributing factor, and successful treatment by manipulation has been performed in some hundreds of cases.

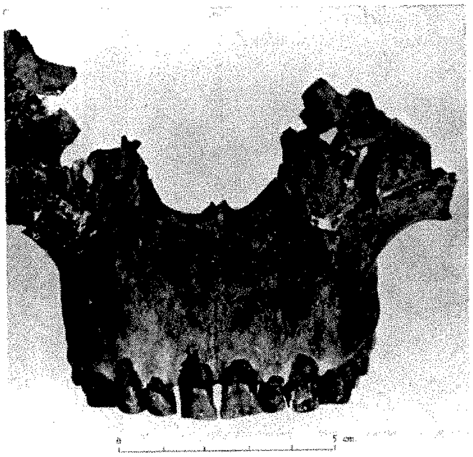


Fig. 14. Maxilla of hominid *Australopithecus boiseii* (1,750,000 years old). Note narrowing and elevation of floor of the left nasal fossa with tilting of the vomer to the right. (Reproduced from *Olduvai Gorge* (vol 2, Fig. 16) by kind permission of the authors P. V. Tobias and L. S. B. Leakey and the Cambridge University Press).

CONSIDERING ANTERIOR CARTILAGE DEVIATION

Table 1 demonstrates not only the significance of pressure with the high incidence in POP, but also the importance of passing right through the pelvic mold as shown by the very low incidence in cases of LUCS. This deviation has been observed occasionally in LUCS, but none was found in this series.

Percentages of Septal Deformity in Infants (Table 1). About 55% of septal kinking was to the left, but no correlation was found with parity, or weight of the baby, or the delivery position.[5] Takahashi,[11] concerning the relationship of right- and left-handedness, fetal position, type of presentation and heredity, found no factor to explain the predominance of left deviation.[7]

Twins appeared to be like single births. Of 15 pairs of monovular or identical twins only four sets (or 26%) had similar septal deformities and of 31 pairs of binovular twins eight sets (or 20%) had similar deformities, i.e., heredity does not appear to be a factor in septal deformity.

Considering Adult Skulls. These were all assessed personally by simple observation, and on "back checking" no discrepancy was found in the original assessment. A considerable number of skulls had to be discarded due to insufficient preservation. A straight septum had no deflection and the vomer was straight. The kinked deformity was obviously to one side, but if the deformity involved both sides (often unequally) it was called deviated (C or S shaped deformity). The posterior border was never displaced, as often observed.[12]

Table 2 shows the results of examination of the ethnic types of European, Indian (Asian), Chinese, African and primitive Australian Aboriginal skulls.

Percentage of Combined Septal Deformity in 2,112 Adult Skulls (Table 2). The incidence of straight septa varied from 13% in the Indian skulls to 27% in the Australian Aboriginals, but the combined total of 21% was practically the same as the 23% that Mackenzie[1] reported nearly 100 years ago. Clinically the Aboriginal and African skulls appeared to be much heavier and have thicker bones than the others, especially the Indian ones. Septal kinking was more common than the deviation except in the Aboriginal series.

It is a commonly accepted observation that the septal spur is more common on the left side (Mackenzie found 58%) and this was supported in this investigation in the babies and adults as shown in Table 3. The question of the laterality of the septal kinking is of little clinical importance, except that there is no doubt of the close relationship of septal deformity with ear disease.[10,13,14]

Percentage of Septal Kinking to the Left (Table 3). The unevenness or elevation of the floor of the nares (Figs. 3, 6, 8, and 9) is easily observable and is a positive sign of the facial deformity and the associated septal deformity, but has no correlation with anterior cartilage deviation. The percentage of uneven external nares is shown in Table 4. In particular, no case of straight septum was associated with unevenness, and all cases of unevenness were associated with some type of septal deformity. If unevenness were associated with kinking, the kinking was always to the opposite side of the elevated nares. X-rays of the sinuses frequently demonstrate this unevenness.

Percentage of Unevenness of Floor of Nasal Fossa in 2,112 Skulls (Table 4). The incidence of unevenness was lowest in the heavy boned skulls, i.e., African, Australian Aboriginal. The association of palatal abnormality, with septal deformity, and in particular the compression and elevation of the palate and floor of the nose on the opposite side of the septal spur, was well-documented and illustrated nearly 100 years ago by Welcker[15] and Schaus.[16] This has been confirmed in this investigation with plaster casts and histological sections, as previously reported.[3-5]

A very close correlation was found of the malocclusion and palate abnormality, as demonstrated by dental models made for 310 cases of rapid maxillary expansion, with the varying types of combined septal deformity which was present in all cases.[17] This association is present from birth as demonstrated in Figures 11 and 12. Figure 11 demonstrates some of the palatal changes. Figure 11 A and B are coronal sections of casts of the maxilla at birth, showing in A, the even symmetrical palate with a straight septum, and in B, asymmetry of the palate with a kinked septum. Figure 11C shows the deformity of the left side of the dome of the palate in a 3½-year-old child, with septal kinking to the right which had been found present at birth. Figure 12 shows malocclusion and crossbite of all the molar teeth on the right in a 2½-year-old child with septal kinking to the left, present since birth. The palate was slightly elevated and narrowed on the right.

To recapitulate, these conditions are easily observed in clinical practice and the results can be readily checked. The difference in percentages of deformity at birth and adult (Tables 1, 2) can be explained and correlated in that strut testing is a comparatively coarse method of testing while the skull examination is accurate. Thus it is reasonable to

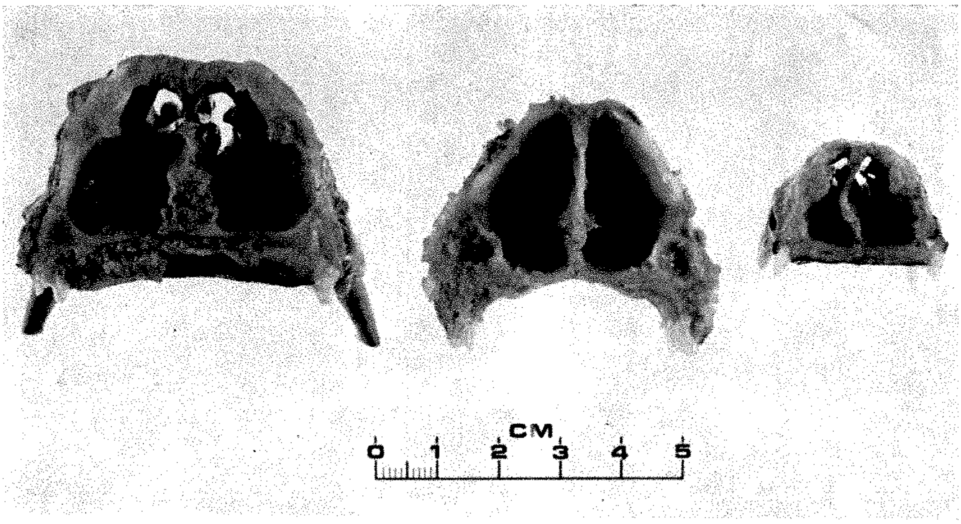


Fig. 15. Dogs' noses, left to right: spaniel, bulldog and Chihuahua-Pekinese cross. Note deformity in the right specimen.

suggest that some of the straight septa (42%) at birth would develop minor irregularity and deformity during growth and be recognized as deformed in the dried skull.

The similarity of the percentages of kinking and deviation in each group, and the continuity of the deformity on reviewing cases, strongly suggest that the deformity of the adult cases had commenced at birth.

The investigation was continued in an attempt to trace the development of septal deformity. Ruffer[18] showed septal deformity in Coptic skulls (400 AD). Figure 13 is an ancient Egyptian skull some 4,000 years old showing typical deformity. A photo in Koenigswald[19] of a well-preserved palate of Neanderthal man (100,000 years ago) shows typical compression and distortion of the dental alignment. Further back, the well-preserved maxilla (Fig. 14) of the hominid *Australopithecus boiseii* – estimated 1,750,000 years old – found at Olduvai Gorge, demonstrates the typical unevenness and narrowing of the floor of the external nares and tilting of the maxillary groove to the opposite side associated with septal deformity.

An investigation of mammals was carried out. Negus[20] stated "It is rare to find any deviation of the septum except in man," although he had found one case in a domesticated dog. Collidge[21] found cranial abnormalities in the gorilla.

In 642 lower mammals, comprising 185 marsupials (kangaroos, possums, koala bears and wombats), 77 wild dogs (dingoes), 33 foxes, 20 lions and tigers and cats, 16 seals and sea cows, 89 domestic dogs and 222 antelopes, only one domestic dog (Fig. 15), a very small Chihuahua-Pekinese cross, had a septal deformity. The occurrence of true septal deformity in this very small snub-nosed dog could be due to selective inbreeding and this type could survive under Post's theory[2] of relaxed natural selection. Of 60 baboons and mandrills, 4 or 7% were deformed, but in the higher apes, of 216 chimpanzees and gorillas, 80 or 37% were deformed (Fig. 16). The septa of the gorillas were often deformed only to a minor degree (? due to the strength of the skull).

CONSIDERING THE MAXILLARY MOLDING THEORY OF PRODUCTION OF SEPTAL DEFORMITY[3-5]

The ensuing sections were obtained from routine postmortems. The noses were strut tested and recorded. The face was then decalcified and sectioned.

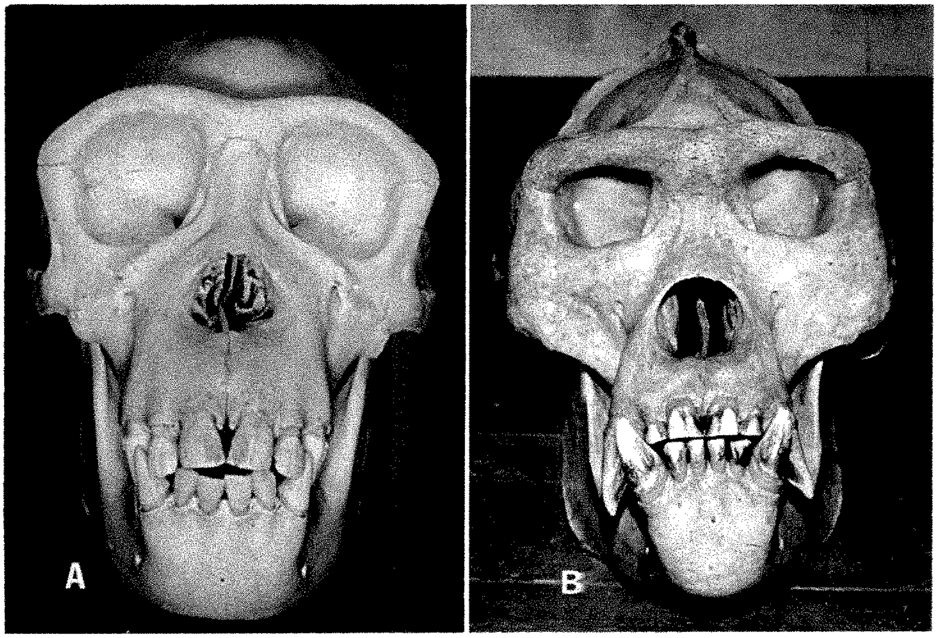


Fig. 16. Primate skulls. A) Chimpanzee skull: note elevation of floor of left nasal fossa with septal kink to right. B) Gorilla skull with deviation deformity.

The septal configurations of the sections were found to correspond accurately to those suggested by the strut testing.

The normal septum is straight and symmetrical, and meets an evenly arched palate in the midline. Figure 17 shows the diagrammatic representation of normal growth of the septum. Figure 18A shows a normal straight septum at birth; note even arch of palate, no distortion of vomer bone and equal sized turbinates on each side, and Figure 18B, a straight septum at six months.

During pregnancy and parturition the fetus is subjected to varying pressures and torsions which may be general or local. The skull bones are soft and readily deformed. Once the skull bones have been deformed and alignment changed, the bones will grow in this altered alignment, because they are not elastic like cartilage and there are no restituting forces except intracranial fluid pressure. Projections of the child or of the mother (such as the nose or coccyx) may cause local abnormalities such as an anterior nasal cartilage deformity or depressed fracture of the skull.[5,22] The transmalar diameter is the widest part of the face, and bilateral pressure (Fig. 19) will be transmitted across each arch of the maxilla, tending to compress the arch causing a cross-bite, and the resultant force will be directed cranially up the septum. If this force is great enough, it will compress the septum against the firm base of the skull, causing splaying out of the cartilage-vomer junction and a bending or a C or S shaped deviation deformity of the septum. Due to the shape of the maxilla and to its firm posterior attachment to the rest of the skull, any changes resulting from even bilateral pressure on the maxilla would be concentrated anteriorly. As demonstrated very well in Figure 20, the maximal splaying out of the vomer and cartilage is anterior, and in this specimen, section of the middle and posterior thirds of the septum demonstrated that there was very little posterior involvement of the vomer. This is the type of deviation deformity (vertical S type) so commonly seen on clinical examination. Angulation of the palate which could occur from these pressures (Fig. 21), is also characteristically associated with this type

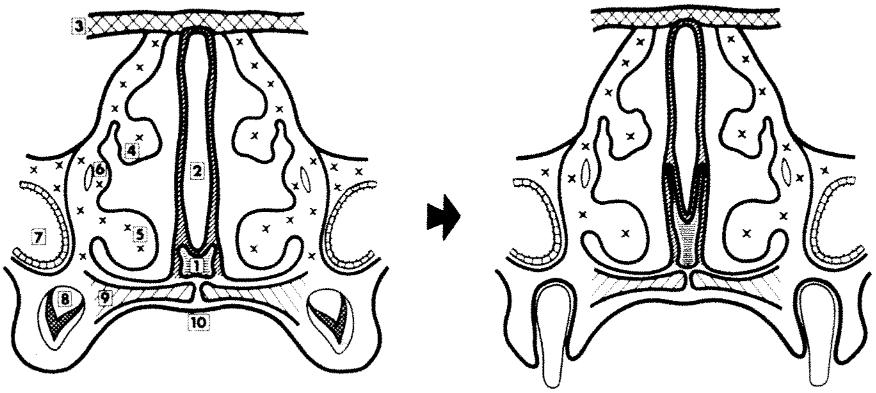


Fig. 17. Diagrammatic representation of normal growth of the septum. 1 - Vomer bone, 2 - Septal cartilage, 3 - Base of skull, 4 - Middle turbinate, 5 - Inferior turbinate, 6 - Ethmoid bulla, 7 - Maxillary antrum, 8 - Developing tooth, 9 - Palatal bony arch, 10 - Dome of palate.

of deviation. Note also the overriding of the incisors. At times the pressure appears to be greater on one side.

Torsion strains may cause inequality of pressure, demonstrated by unequal parietal bone molding (Fig. 2). If the compressing force acts more on one side (Fig. 22), that side of the maxilla will tend to be compressed medially, causing malocclusion of the teeth and crossbite, and the palate will be narrowed and raised on that side, thus tilting the vomer to the opposite side and causing kinking of the ethmoid-vomer junction. (This has been well-shown by a palate-septum model.[5]) Figure 23 demonstrates this at birth. Note that the turbinates are equal. Figure 24 is a child aged six months demonstrating the elevation of the palate, tilting of the septum with spur formation to the opposite side. Note the abnormal growth of the vomer bone by this age, the unequal size of the turbinates, and in particular the compensatory overgrowth of the turbinates on the concave side of the septum and the increase in size of the ethmoid bulla on that side. Figure 25 shows the characteristic combination of unilateral palate compression and abnormal external nares in a girl aged 12

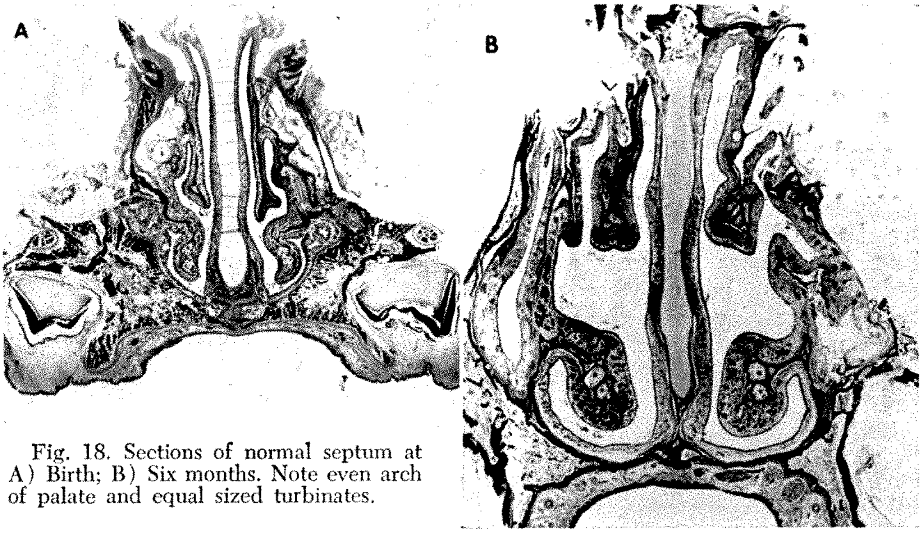


Fig. 18. Sections of normal septum at A) Birth; B) Six months. Note even arch of palate and equal sized turbinates.

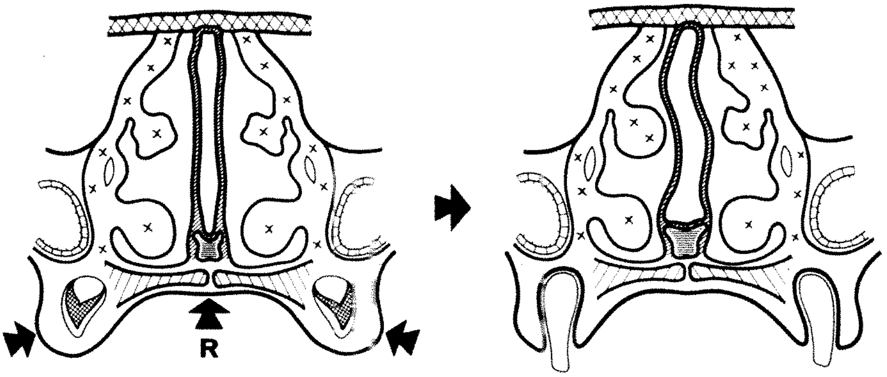


Fig. 19. Diagrammatic representation of growth following bilateral pressure (arrows) on the outside of the developing teeth. This causes arching and compression of the palate, and the resultant force (R) being transmitted up the septum against the firm base of the skull. This compresses the septum and causes splaying out of the cartilage-vomer junction. With growth, compensatory hypertrophy of turbinates and side wall of nose opposite any septal concavity occurs, while there is normal growth of the vomer bone up each side of the cartilage.

years, and septal kink to her left the opposite side).

The dental changes vary with the site of compression, or torsion strain and may be localized over a) incisor area b) canine area (Fig. 26), c) molar area (Fig. 12) or d) be bilateral. If the compression is localized over the incisor area, the incisors are angled a little posteriorly with protrusion laterally of the canine teeth, and usually angling backwards of the lower incisors; and the septum usually has an anterior deformity and a deviation. If localized to canine or molar area there is a kink deformity to the opposite side. If bilateral compression is evident, then septal deviation to both sides, has been found to be present. The mandible may swing to either side to improve the bite on the cusps of the teeth, and this aggravates the crossbite. Thus this is a major cause of malocclusion.[9,17]

This local compression may cause homolateral flattening of the cheek. If

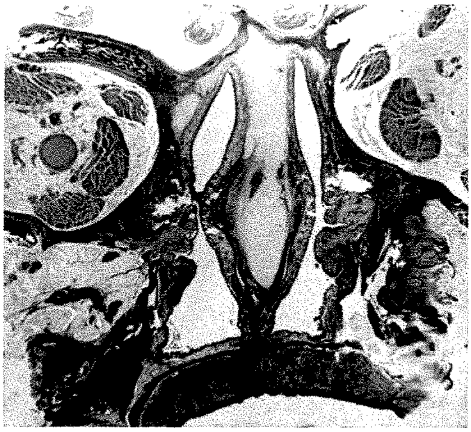


Fig. 20. Section of anterior part of system at birth with obstruction to both sides on strut testing. Note the compression of septum with distortion and fracture of the cartilage.

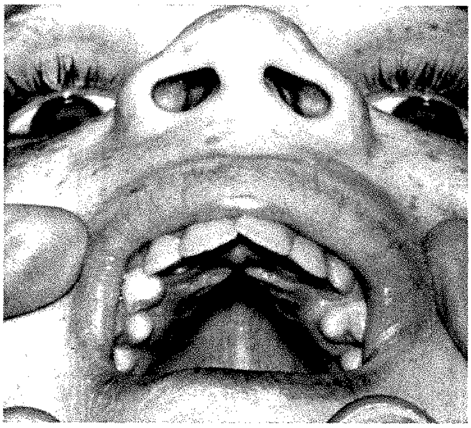


Fig. 21. Bilateral compression. Photo of teeth and mouth of 12-year-old with deviation or compression deformity of the septum. Note the even acute angulation of the anterior end of the palate and the even shaped external nares.

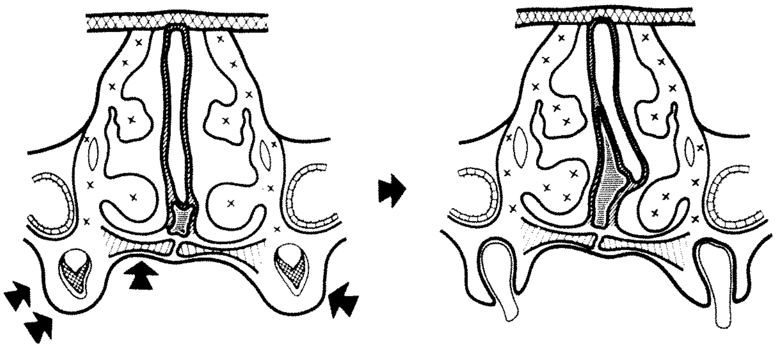


Figure 22.

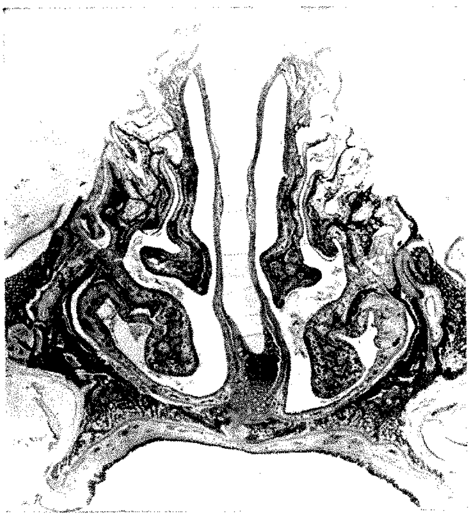


Figure 23.

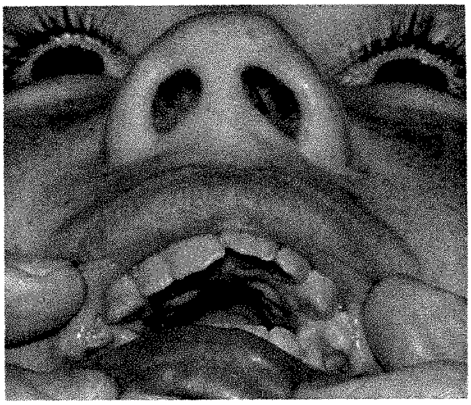


Figure 25.

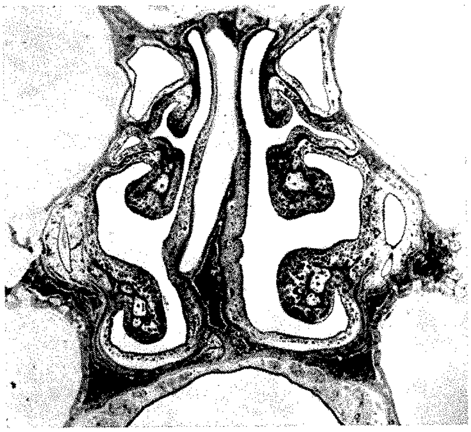


Figure 24.

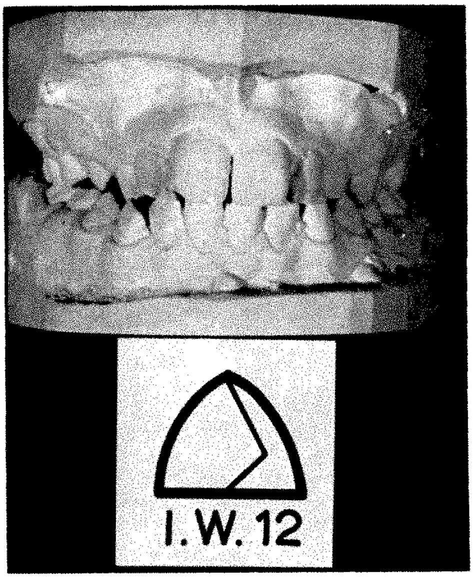


Figure 26.

the compression is over the canine area, the external naris is flattened, but if it is to the side, over the molars, the shape of the naris becomes rounder and less elongated due to the pressure from behind (Fig. 25). There is usually a corresponding dental deformity. This deformity of the nares is quite different from that associated with anterior cartilage deviation.

It is stressed that this is a facial deformity with varying degrees of dental malalignment, palatal changes (bilateral narrowing and angulation anteriorly, or unilateral narrowing), change in shape of cheek and external naris, changes in the lateral wall of the nose and finally septal deformity.

The fetus is pushed through the pelvis and it rotates to follow the line of least resistance. There is continued pressure exerted during the birth and this pressure on the parts of the skull must vary at different stages (torsion pressure) to make the head rotate. The constancy of the figures (Tables 1, 2) suggests that with each racial type of skull (shape and structure), this pressure will cause all variations between no changes, or straight septa, to considerable deformity. The type of deformity will depend on whether the variable pressures act mainly bilaterally or unilaterally and also on the site of maximum pressure.

Experimental work on rabbits by Wexler and Sarnat[22] on kinking of the vomer cartilage articulation support this method of production of septal deformity.

By the age of two the height of the nasal cavity is one-half that of the adult, and by the seventh year is two-thirds that of the adult.[23] Up to the third year increase of height is by growth of the cartilage of the septum thrusting the maxilla downwards and forwards. After that, the increase of height is by resorption of the upper surface of the palate and deposition of bone on the under surface. Thus the septal growth is controlled by the opposition of the cartilage and vomer bone. In cases of bilateral pressure and simple deviation deformity there is no loss of these controlling opposing pressures and the deformity does not increase with age. In cases of unilateral pressure and kinking there is loss of this opposing pressure and the kinking tends to increase with growth, with the cartilage tending to overgrow the groove of the vomer. The perpendicular plate ossifies and becomes united to the vomer by the seventh year.

DISCUSSION

Mackenzie,[1] referring to septal deformity in his Manual, reported the following findings of Zuckerkandl.[24]

1. The septum is always straight before the seventh year.

2. The superior races show a greater disposition to this deformity than those of a lower type.

These statements are still frequently quoted in textbooks and accepted in the

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Fig. 22. Diagrammatic representation of growth following unilateral pressure. Note elevation and pushing in of the maxilla on the left, the development of the spur deformity on the right, with abnormal growth of the vomer up one side of the cartilage on concave side of the spur with compensatory hypertrophy of the turbinates and enlargement of the ethmoidal bulla on that side. Note also change in alignment of the teeth on the left.

Fig. 23. Section of septum at birth (viewed from the front) with unilateral obstruction on the left on strut testing. Note elevation of right side of palate, tilting of vomer to the left and equal size of turbinates.

Fig. 24. Section of septum of baby aged 6 months (viewed from the front) with unilateral obstruction on the right on strut testing. Note elevation of palate on the left side and abnormal growth of the vomer up one side of cartilage on concave side of spur. Note now the development of hypertrophied turbinates on left and enlargement of the left ethmoid bulla.

Fig. 25. Unilateral compression. Photo of 12-year-old girl with septal spur to her left. Note compression of palate and teeth on the right and difference in shape of external nares considered to be from pressure on most of the cheek at birth.

Fig. 26. Dental changes showing local compression over canine area with septal spur to opposite side.

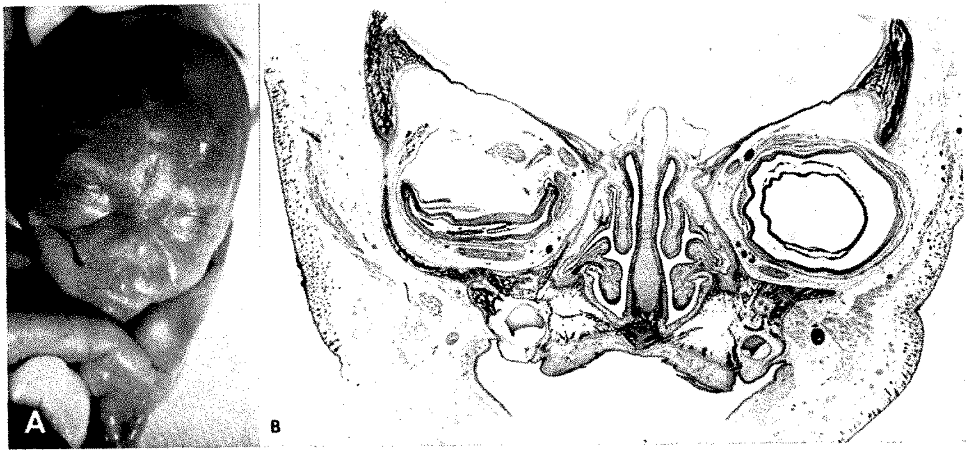

Fig. 27. A) Abnormal arm position across the cheek in a 5-month fetus. B) Microscopic section showing indentation of cheek from pressure on that side by the arm tending to splay out the face, with elevation of the floor of the brain, and pushing down of the palate with early tilting of the vomer-cartilage junction.

literature. For example, Cunningham[25] refers to the septal spur, stating, "As a rule it is not developed until after the seventh year," and Post[2] found some increase in frequency of septal deformation in "civilized," as contrasted with "primitive" populations.

The work reported in this paper demonstrates that not only is septal deformity commonly present but is present in a remarkably constant degree, both at birth and in the adult.

Increased parturition pressure[7] (Table 1), particularly across the malar bones, undoubtedly causes increased deformity. There is still a considerable incidence in cases of caesarian section, thus parturition pressure is only part of the cause and additional factors must occur during pregnancy. Firm pressure or quite gentle forces, if persistently applied, will readily distort the soft cranial bones of the developing child. Once distortion and change of alignment have occurred, there are no forces acting to return the alignment to normal (apart from intracranial pressure). Abnormal posture pressures undoubtedly can occur, as demonstrated in a five-month fetus with an abnormal posture of one arm across the cheek (Fig. 27A). The section (Fig. 27B) shows a splaying out of the face with elevation of the floor of the brain and depression of the palate, narrowing of the labiogingival sulcus and tilting of the vomer-cartilage junction. This tilting would cause septal deformity with growth due to loss of septal controlling pressures. The influence of oligoamnios increasing postural deformities by limiting the free movement of the fetus, has been well-documented.[26] Pressure of the head on the pelvic rim would be aggravated by gravity and lax abdominal muscles.[27] These gravitational pressures do not affect the quadruped, as the developing fetus is supported by the soft abdominal muscles and suspensory ligaments, and does not become engaged in the pelvis until parturition.

Change of shape of the skull with evolution, with development of the maxillofacial skull since Neanderthal man, has been suggested as a factor.[28] Metzenbaum[29] stated that in most vertebrates from the serpent to the ape, the two nasal bones extend down to the end of the nose, protecting the septum. In the higher ape and man, the nasal bones cover only from the frontal bone to the end of the nasal portion of the maxilla, and most of the septum is in the skull itself, and will be affected almost only by transmitted pressure. The exposed anterior cartilage may be affected by direct pressure.

Although in mammals the head bears

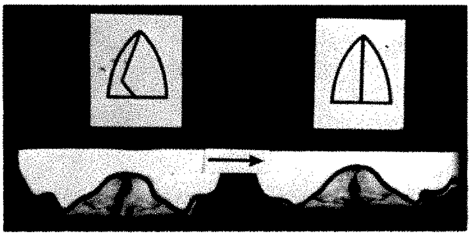

Fig. 28. Palatal casts, cut coronally about the middle, of a 3-day-old baby taken before (left) and immediately after (right), manipulation. On the left note how the palate had been pushed in on the right with the septum kinked to the left (on strut testing). The cast on the right demonstrates the change in shape of the palate and now is nearly symmetrical after manipulation. The testing struts now passed easily down both nostrils.

the major brunt of dilating the birth passages, in the lower animals, the pointed snout takes little part in this dilation. As the septum in the snout is protected by bone, little septal deformity should occur.

Heredity is unlikely to be a factor particularly as septal deformity occurs in about 75-80%[1,5] of the population, and also considering the lack of correlation with monovular and binovular twins. The shape of the palate appears to be genetically controlled, for similar outlines can often be seen in families. However, similar septal configuration, straight or deformed, can occur with a high arched or a flat palate. It is not unreasonable for a similar septal deformity to be present in some siblings, for they all have to pass through the same maternal pelvic mold.

The Australian Aboriginal skulls in this survey were all "primitive" and had not been associated with white man's diet and were the least deformed. The size and shape of the palate and mandible in European skulls have altered over the last 2,000 years, with the change to a soft diet being considered a major factor.[30,31] I consider it is the shape and strength of the skull which are important, rather than the degree of "civilization."

These findings give a rationale to treatment, by manipulation and rapid maxillary expansion.

METHOD OF MANIPULATION[4,5,32]

Anterior Cartilage Deformity. Manipulation using special infant septal forceps (modified Walsham forceps with blades 17 mm long by 6 mm wide by 2 mm thick)[32] is performed by first elevating and manipulating the nasal bones, then the cartilage and tip of the nose are lifted up and the cartilage swung back into position on the groove of the maxillary spine. The mother then applies lateral pressure on the side of the nose to keep it reduced, for five seconds after each feeding for five days.

Combined Septal Deformity. The infant septal forceps are passed well into the nose, and the middle of the palate is pressed caudally and downwards firmly for 15 to 20 seconds to reduce the initiating deformity. (The posterior end of the septum is always straight). This also tends to expand the maxilla, reducing its deformity and to pull the septum straight. The septum is then manipulated to the midline. This can be done satisfactorily (with increasing difficulty however) up to the age of nine months or so. Figure 28 demonstrates both the improvement in alignment of the septum as found by strut testing, and in the symmetry of the palate with manipulation in a 3-day-old baby.

RAPID MAXILLARY EXPANSION[9,17,33]

This is performed by cementing an expanding device to the upper back teeth. The screw is turned daily for three weeks and the maxilla opens at the midline by about 8 mm. This greatly improves the airway in some 80% of cases,[9,17] tends to improve the dental occlusion and depress the center of the palate, thus pulling the septum straight. The device is removed in 2-3 months and replaced by a simple retaining dental plate thus preventing relapse.

These findings suggest that:

1. Varying degrees of septal deformity occur at a constant rate at birth and in the adult for each ethnic type.

2. Pressure on the head may occur either a) during pregnancy, caused by gravity causing pressure on the bony

pelvis and abnormal fetal posture (aggravated by oligoamnios), or b) during parturition, varying with the type of presentation.

3. The birth molding pressures are a major cause of dental malocclusion.

4. This concept enables easy recognition at birth and a rational method of treatment by manipulation[4,5,32] and rapid maxillary expansion.[9,17]

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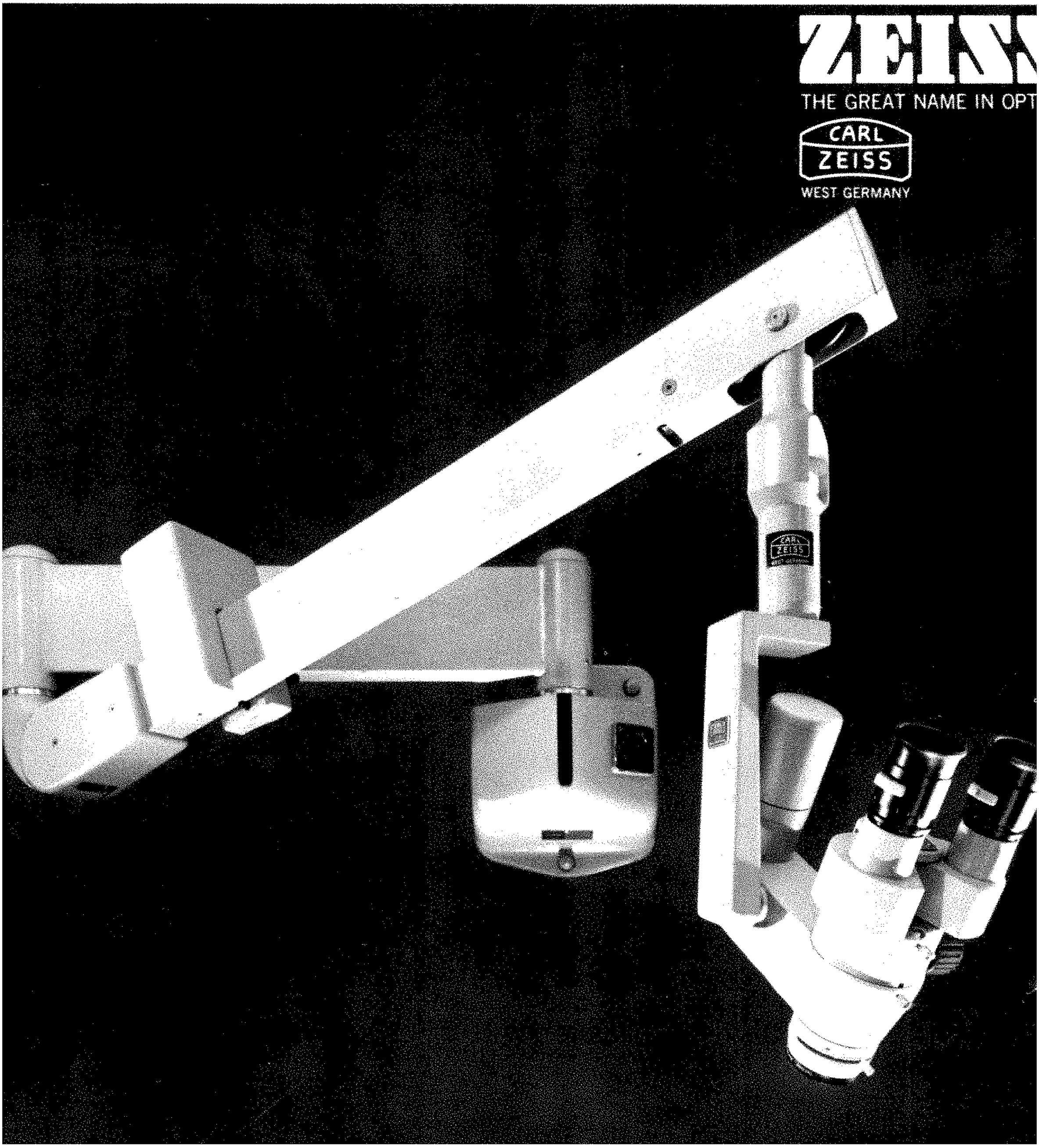

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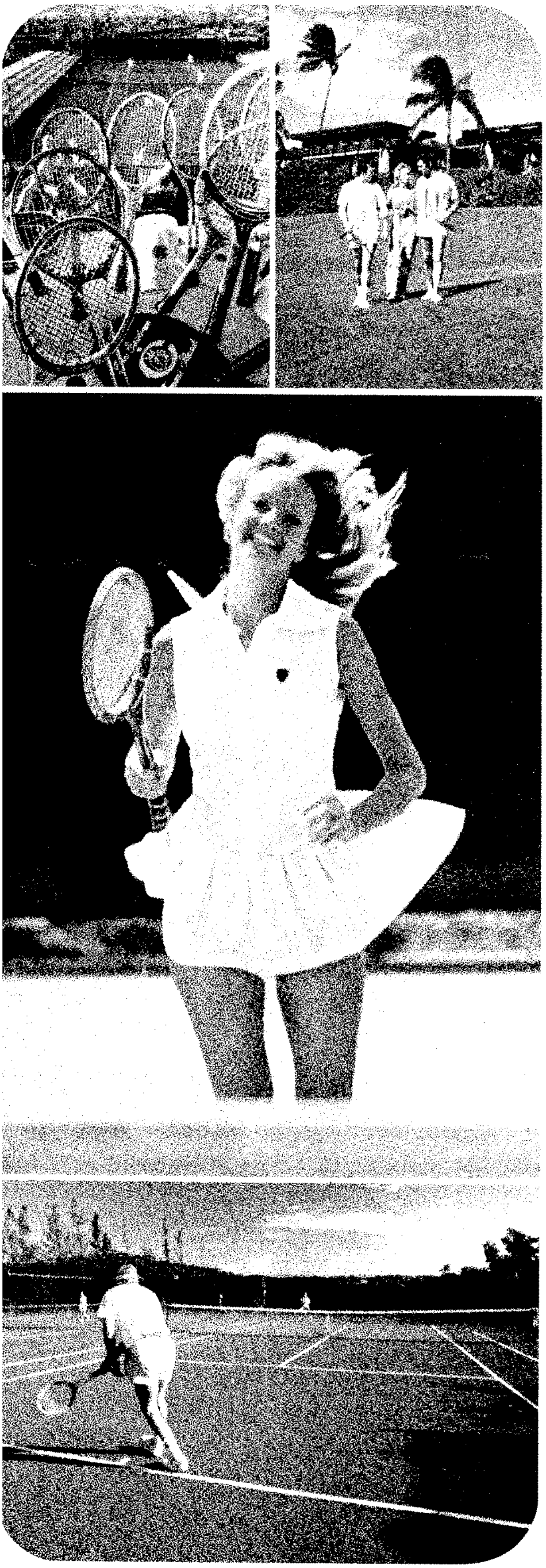

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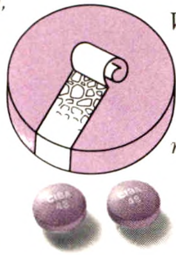

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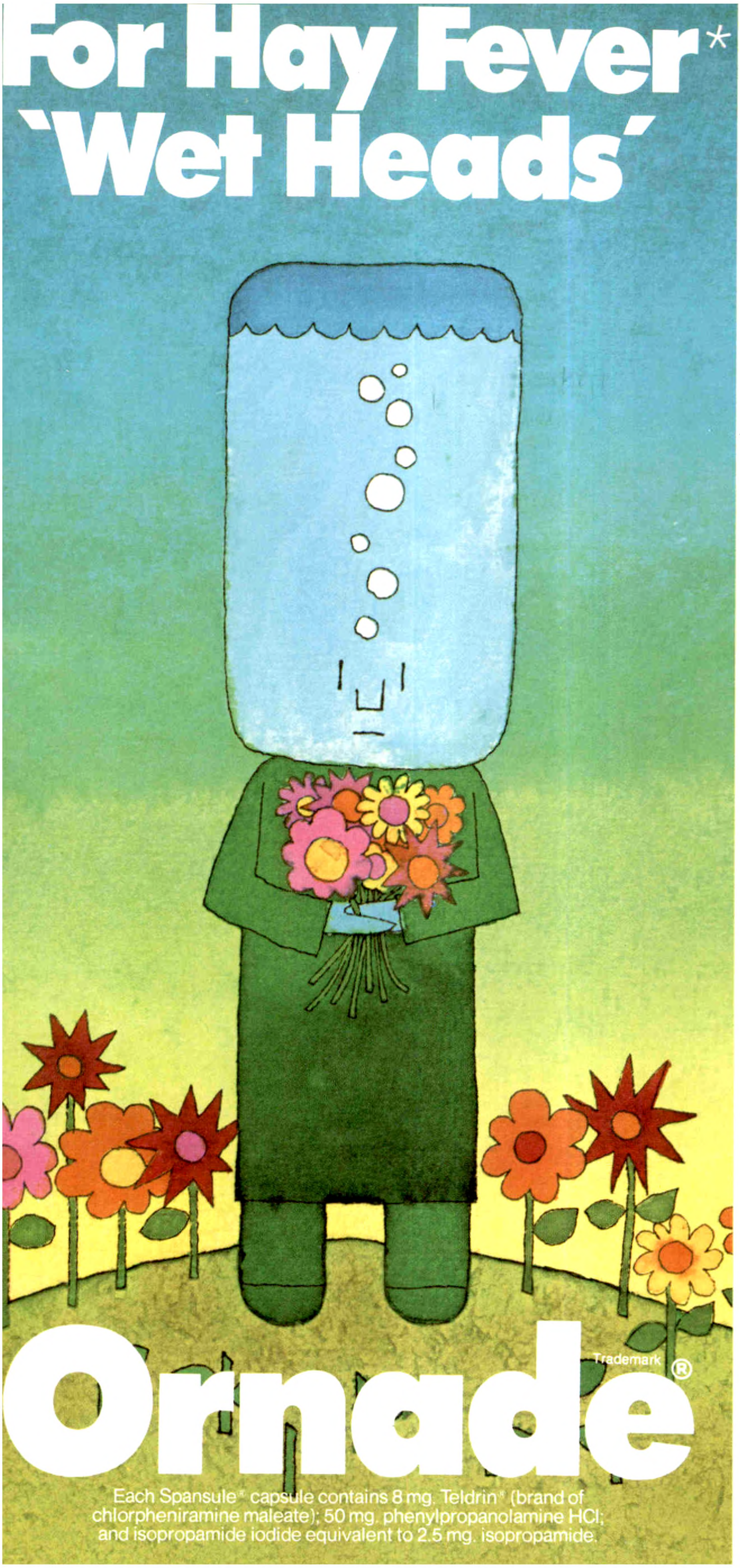

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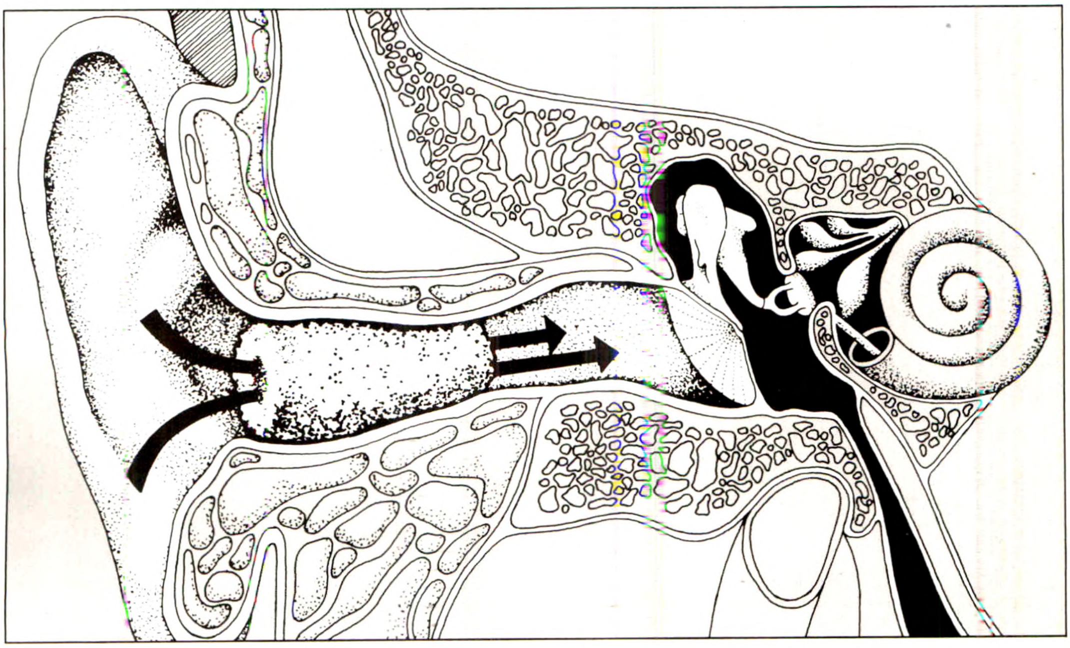

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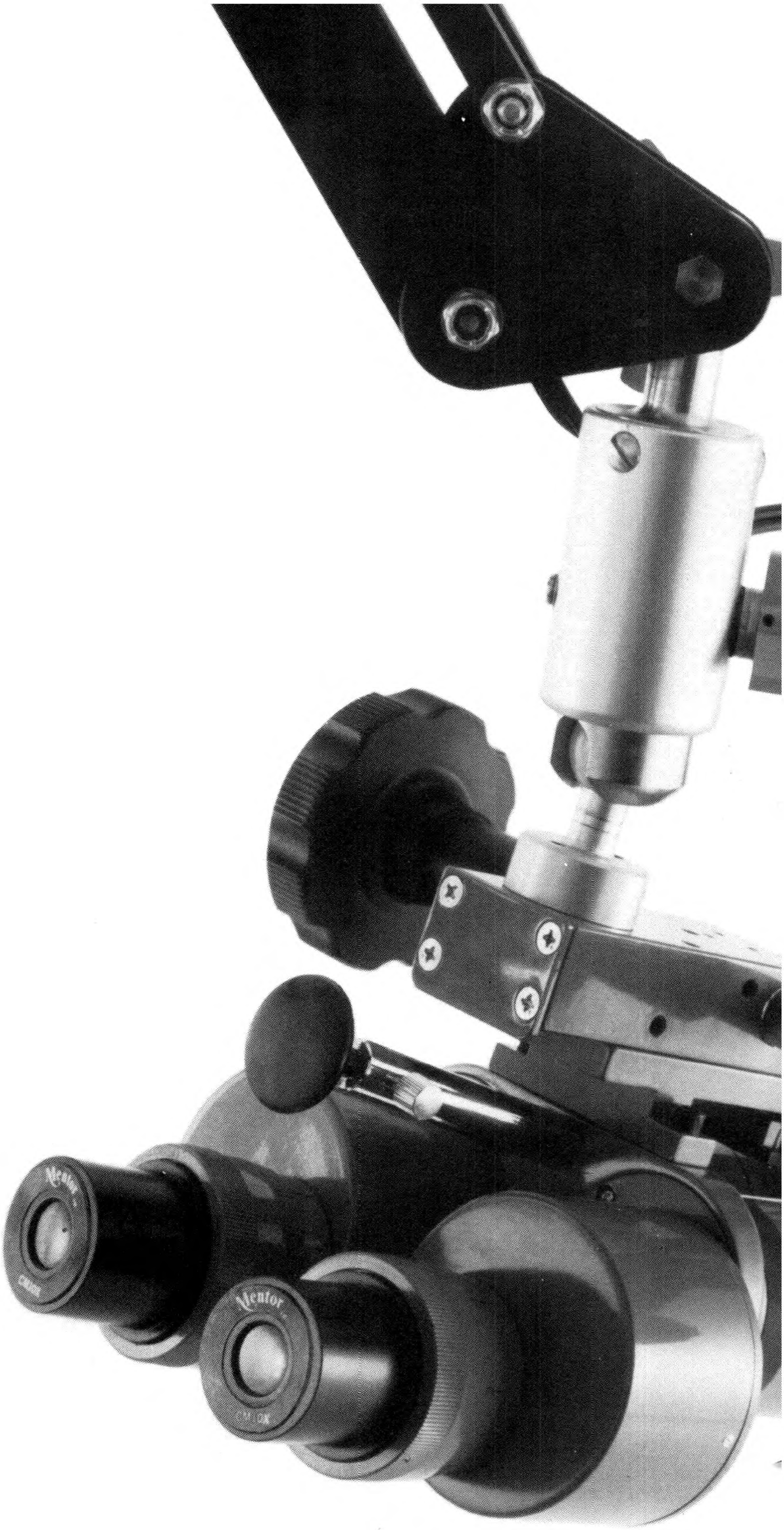
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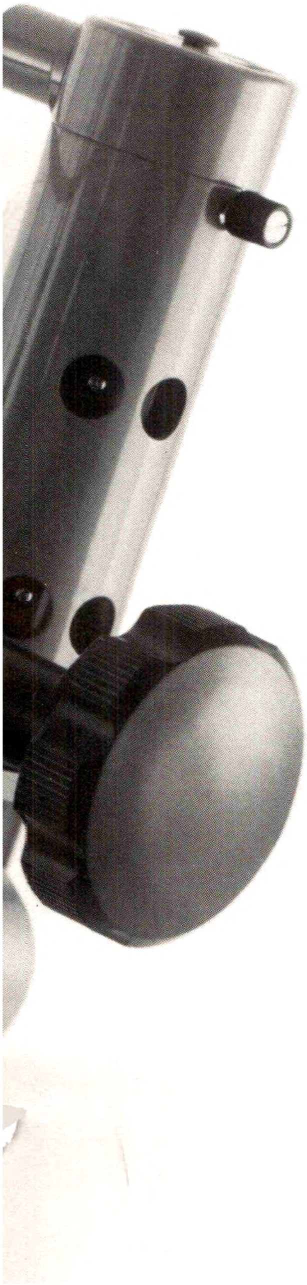

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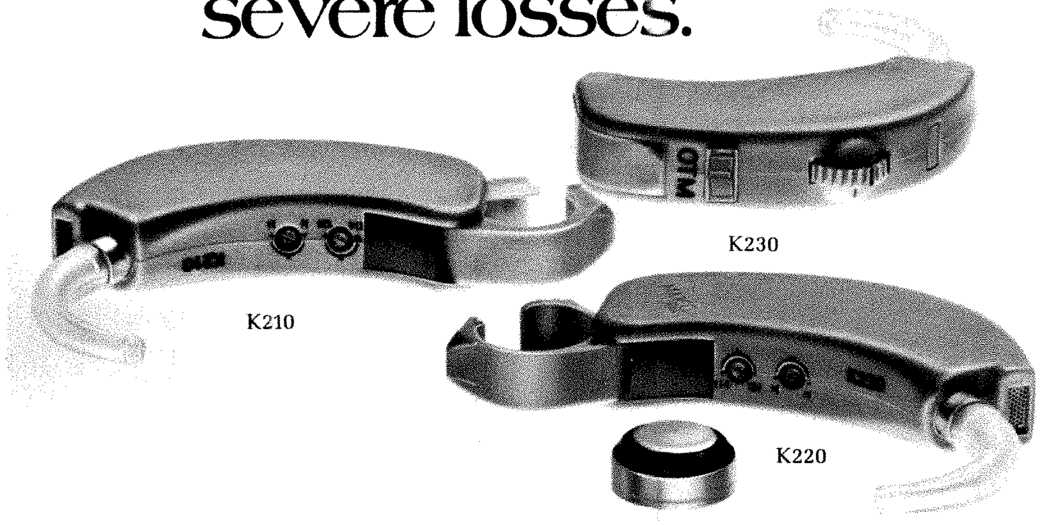

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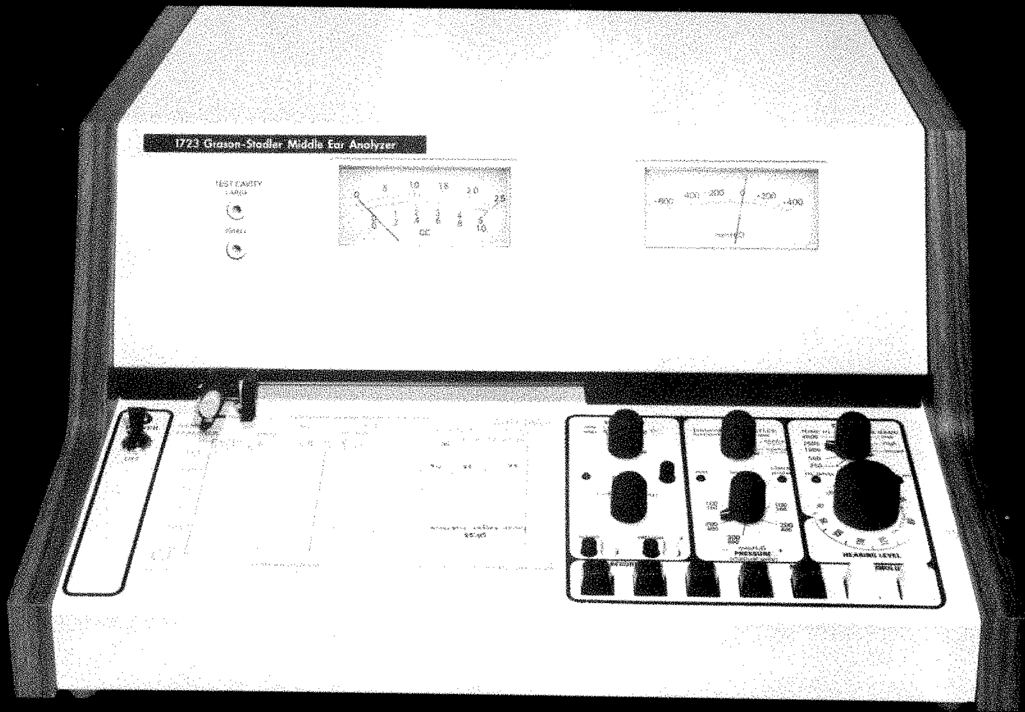

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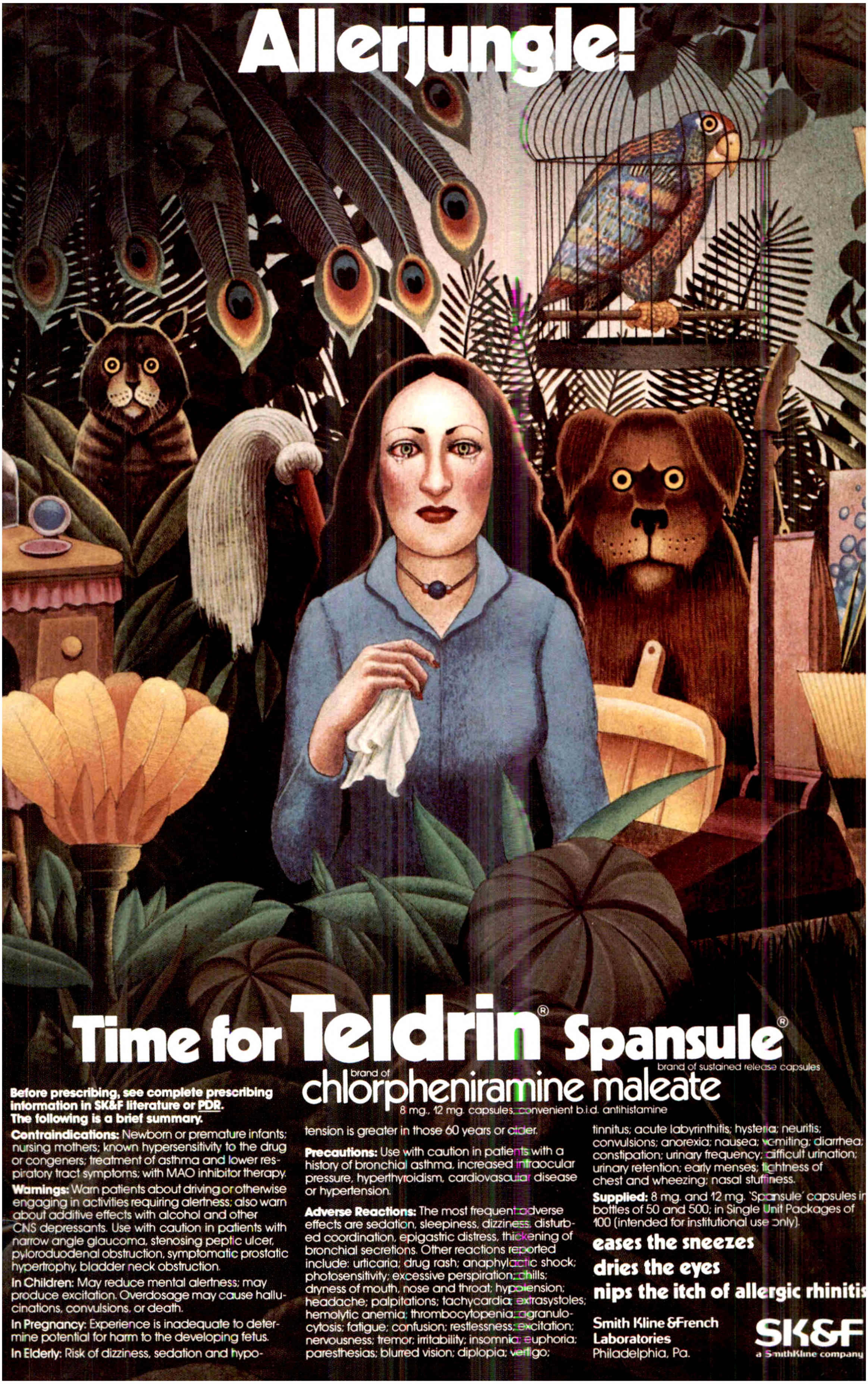
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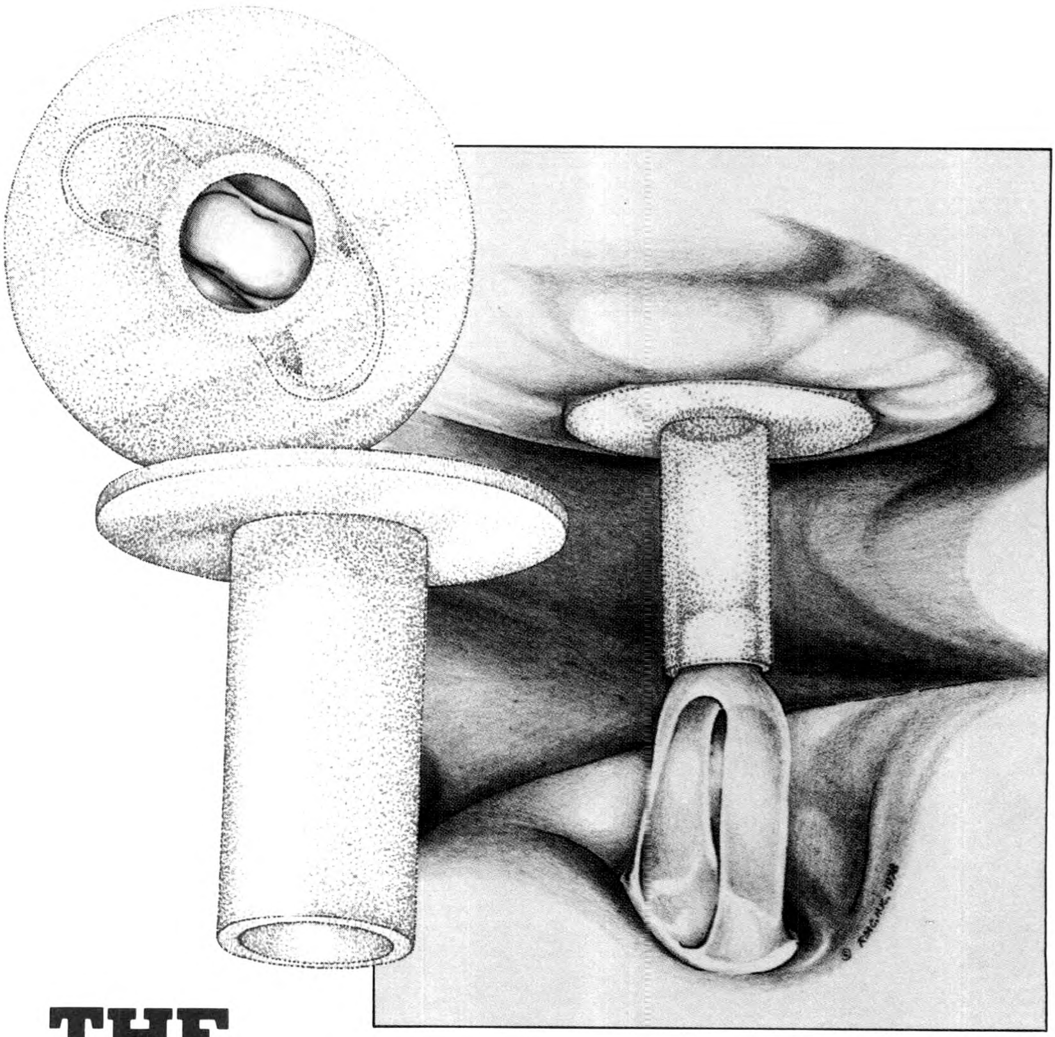

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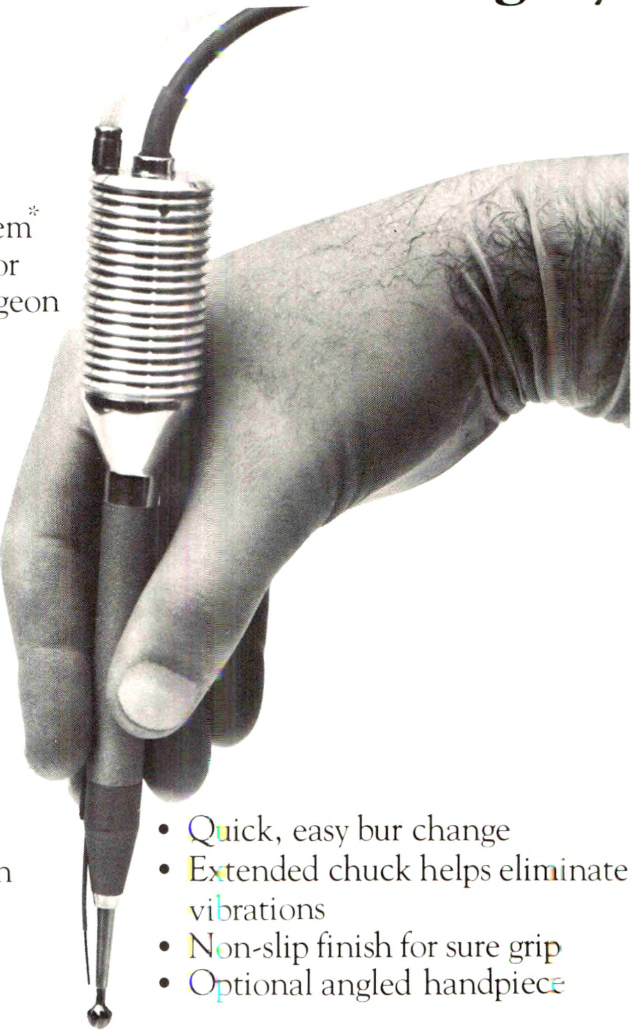

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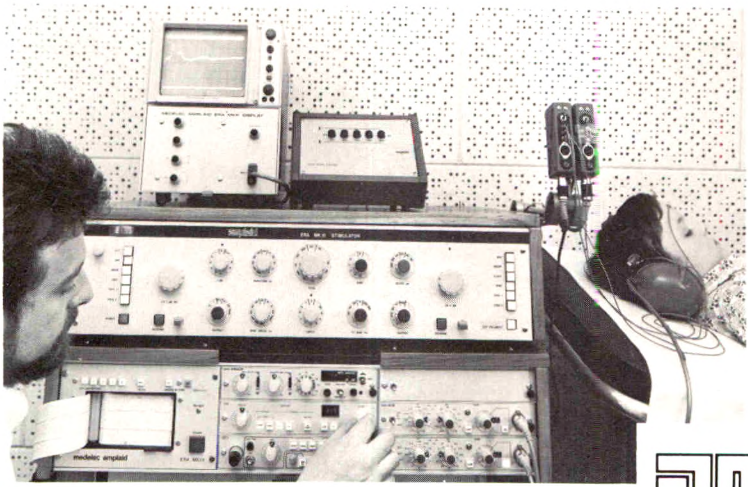

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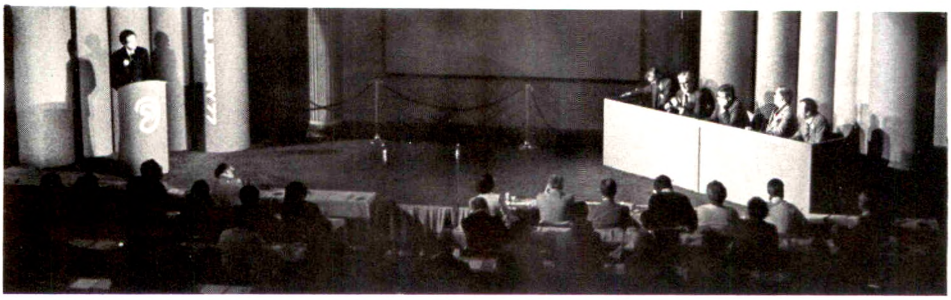

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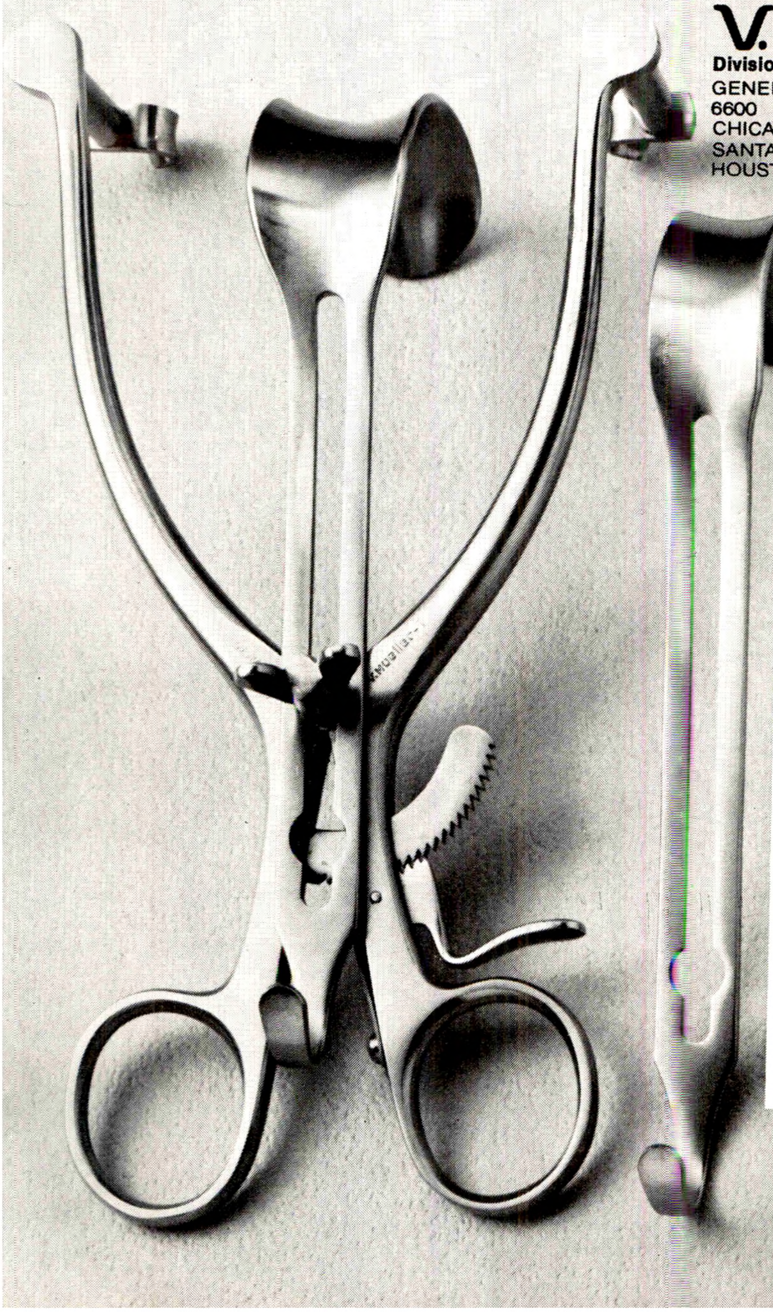

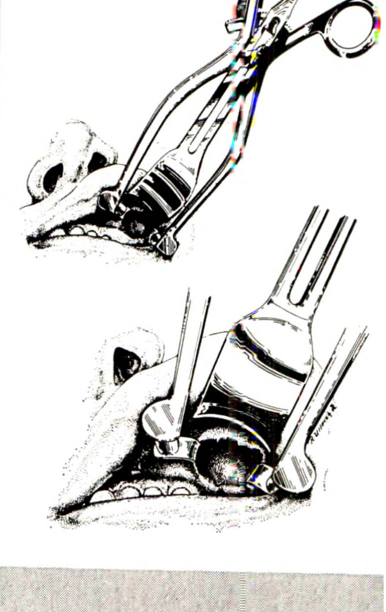

ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY
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Ann Otol 87:1978

CHEVALIER JACKSON LECTURE

ANALYSIS OF NEW OPTICAL SYSTEMS IN BRONCHOESOPHAGOLOGY

GEORGE BERCI, MD
LOS ANGELES, CALIFORNIA

A new image transmitting system (Hopkins rod lens) made it possible to redesign the entire armamentarium of rigid broncho- and esophago- laryngology. The introduction of an optical biopsy forceps made tissue sampling more accurate. The increased light transmission produces a brighter image and easier perception. The larger viewing angle facilitates orientation. The new miniature pediatric bronchoscope, with a telescope, changed the pinpoint vision to a panoramic view. The optical foreign body forceps is of great help in fast and precise manipulations. The indirect laryngoscope proved to be a great investigative tool with the capability to obtain, with ease, a movie filmstrip for detailed analysis in the outpatient clinic. The introduction of the flexible fiber bronchoscope brought new dimensions in tissue sampling of peripheral lesions, treatment of pulmonary complications in the intensive care units, and became an important aid in intubating patients with difficult anatomy. The possibility to obtain movie films and to study our visual findings, at leisure, is an important diagnostic and teaching aid.

It is a great honor and privilege for me to deliver the Chevalier Jackson Lecture.

Twenty years ago I became interested in the endoscopic inspection of the bile ducts during surgical exploration of the biliary system. The first telescope which I selected was the cystoscope, thinking that this was one of the endoscopic instruments most frequently employed and therefore supposedly best developed. It took me one year to find out that although the optics were improved, the basic principle was essentially the same since 1879 when Nitze described his first cystoscope.[1] The performance of the available telescopes was extremely poor in efficiency of light transmission and in image quality. After an extensive search, I finally found a physicist (Dr. H. H. Hopkins) who not only believed in the validity of the criticism, but who also came up with an idea which constituted a significant breakthrough in endoscopic procedures of the larynx, bronchial tree, and esophagus, and opened new vistas in the field of pediatrics.[2]

Our endooptical armamentarium is divided into three major groups: 1) rigid endoscopes, 2) flexible endoscopes, 3) miniature endoscopes.

RIGID ENDOSCOPES

The invention of the rod-lens optical system by Hopkins (Fig. 1) was a major impetus for redesigning a completely new set of instruments which permitted us not only to see more and to operate with greater accuracy, but also to document our findings in the upper respiratory tract. The great advantages of these new image transmitting systems are: increased light transmission, brighter image (and easier perception) and wide viewing angle. Therefore a larger part of the organ can be seen in a single viewing field with minute detail, which in turn facilitates faster and more accurate orientation. Another feature of this new image transmitting system is that with miniaturization, for instance in a pediatric size, the superb image quality is still maintained, something impossible to achieve with the standard lens system. Because of the vast improvements in light transmission, resolution, depth of field, color reproduction and other factors, we were able to obtain excel-

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From Cedars-Sinai Medical Center and UCLA Medical Center, Los Angeles, California.

Presented at the meeting of the American Broncho-Esophagological Association, Palm Beach, Florida, April 24-25, 1978.

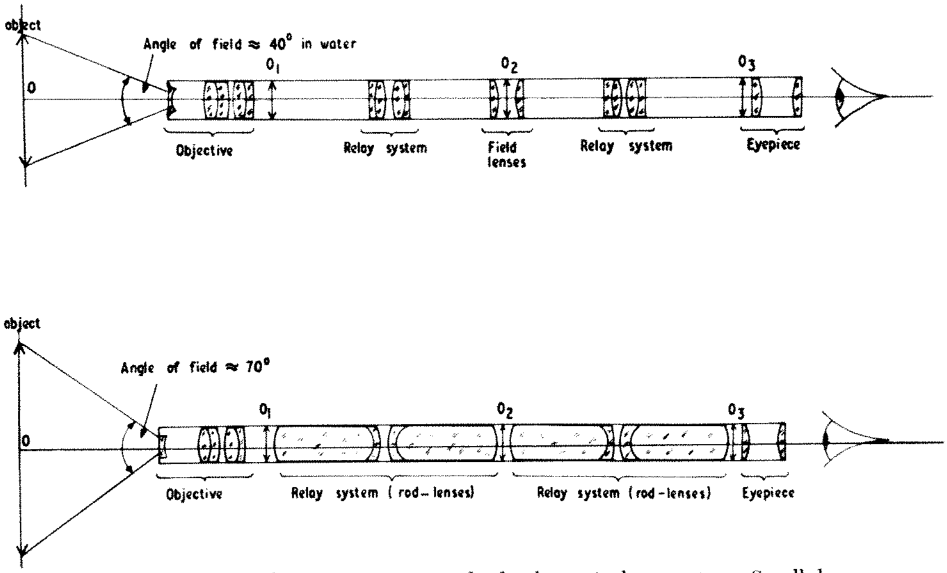

Fig. 1. Schematic diagram. Top: Standard telescopic lens system. Small lenses are placed in certain air intervals. A significant portion of the image (light) is absorbed. Bottom: Hopkins rod-lens system. Small glass rods replaced the previous air interspace. Tiny lenses are cemented at the end of these rods. Image (light) transmission is significantly increased. For detail see text. (From Hopkins HH: Optical principles of the endoscope, in Berci G (ed): *Endoscopy*. Courtesy: Appleton-Century-Crofts, New York, 1976.)

lent still, movie, and television displays through these telescopes.

It is surprising that although several million endoscopic examinations are performed per year in the United States alone, basic research studies of this important diagnostic method are rare in current literature. It took years of experimenting before a laboratory prototype could be converted to a useful clinical tool. We were able to report our first successful results in the field of urology in 1969.[3]

Indirect Laryngoscopy. The laryngeal mirror is a common and well-known method of examination of the larynx or vocal cords and has become a symbol of our profession. It is simple and inexpensive but has many drawbacks. Despite the image being reversed we have become used to it. The light and image is transmitted *through the same mirror* causing a disturbing reflection. The mirror and the head reflector must always be aligned, the size of the object seen is small and the mirror must be moved around to cover the entire area of the larynx. The vocal cords produce extremely fast movements during phonation, so that slight impairments can escape detection, since only a fleeting glimpse is available to inspect function. Short and fast changes are difficult to recollect. It is extremely cumbersome to obtain a permanent record taken through the mirror to be able to analyze the findings.[4]

An indirect laryngoscope was developed which consists of a right-angled telescope inserted in a light carrying sheath (Fig. 2). The outside diameter (8 mm) is smaller than a standard laryngeal mirror. A minimum amount of air can be puffed in the front of the lens by means of an aquarium pump or oxygen outlet, providing positive pressure to avoid fogging. It can also be immersed in warm water for the same purpose. It is easily introduced in a nonanesthetized, seated subject, as an outpatient procedure, in a manner similar to introduction of the mirror. The *entire* anatomy of the larynx can be seen in *one single viewing field* with a view magnified and bright. Lesions as small as 0.5 mm or less can be discovered.

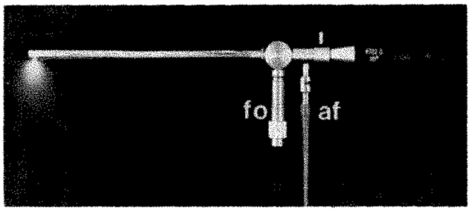

Fig. 2. Indirect laryngo-nasopharyngoscope. Outside diameter: 8 mm. Smaller than the laryngeal mirror. Direction of view: 90°. The entire larynx and vocal cords can be seen in one enlarged view. Turning the scope 180° around, the nasopharynx will come into view. af - Antifog tube connected to an aquarium pump or oxygen outlet provides positive pressure in front of the objective to avoid fogging. fo - Fiber optic cable.

In those patients where the laryngeal mirror can be introduced without topical anesthesia, this instrument, too, will be accepted in the same manner. If an interesting organic or functional disorder is discovered, a still or movie camera can be attached and within a few minutes a movie filmstrip can be obtained from the patient during normal respiration and forced phonation.[5] In case of a movie filmstrip, it can be repeatedly screened, using an analytic projector, at leisure, without the necessity of having the patient present.[6] Slight impairments overlooked at first inspection can be discovered by repeated slow motion analysis. Many innervation problems were overlooked using the standard mirror technique.[7,8]

As for teaching, it is very difficult to observe the mirror image of a lesion, over the shoulder of the examiner. Using a telescope with a teaching attachment, which consists of a beam splitter coupled to a telescope, simultaneous observation is possible without overtaxing the patient (Fig. 3).[9,10]

Posterior Rhinoscopy. The mirror examination of the posterior nasopharynx is even more difficult than the larynx because the size of the mirror is very small. The above mentioned disadvantages of the mirror examination (larynx) are enhanced in this area. Rotating the previously described indirect laryngoscope 180°, a wide angled view of the posterior nasopharynx can be observed as shown.*

Adult Rigid Bronchoscopy. It was evident to Edwin Broyles as long as 60 years ago, that a telescope introduced in a bronchoscope sheath will correct our tunnel vision to a more naturally oriented one. With the introduction of the rod-lens system, employing three telescopes of 0° straight forward, 30° forward oblique, and 90° lateral, the inspection of the bronchial tree, using an open tube system, but with a telescope and documentation facilities, we have been provided with a significantly improved diagnostic modality. Modern metallurgy has made it

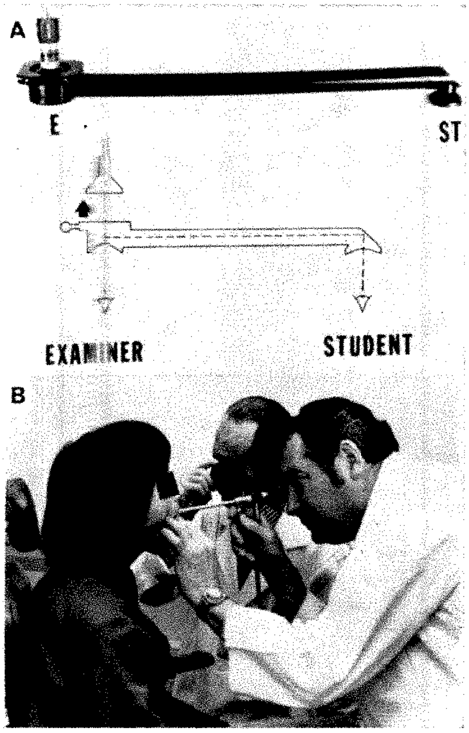

Fig. 3. Coupling a teaching attachment to the telescope, simultaneous observation is possible. A) Telescope. E - Examiner ST - Student observer. B) Examination of patient. (From: Ward PH, Berci G Calcaterra TC: Indirect endoscopic examination of the larynx and nasopharynx in Berci G (ed): *Endoscopy*. Courtesy: Appleton-Century-Crofts, New York 1976.)

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*A 16 mm movie filmstrip was displayed, showing various organic and functional disorders of the larynx and nasopharynx.

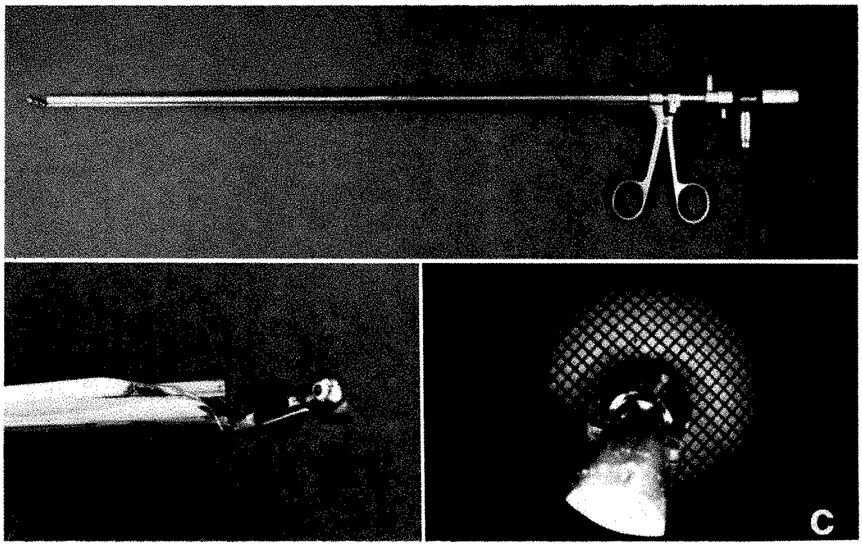

Fig. 4. The optical biopsy forceps. a) The telescope is inserted into the forceps. b) Working end in close-up. c) The actual movements of the jaws can be accurately observed. The closure of the jaws does not obscure vision.

possible to employ tubes with a thinner wall, but with the same outside diameter, resulting in a larger lumen.

Optical Biopsy Forceps. To take an accurate tissue sample of any visible pathology is one of the goals of any endoscopic examination. Using an open tube system the lesion can be seen, but if the biopsy forceps is introduced, vision is partially obscured. The actual manipulation is performed *semiblindly*. In general our best chances are the first bite because the consequent oozing of blood makes further repeated manipulations more difficult.

The optical biopsy forceps consists of a telescope to which a sharp cup forceps is attached and is introduced in a position to enable us to see the lesion as well as the actual movements or placement of the cup of the forceps (Fig. 4a, b, and c). The rigid biopsy forceps can be used in conjunction with the 0° (straight forward) or 30° (forward-oblique) telescope. The upper lobe orifices can be very well-visualized through the 90° (lateral) optics. A remote controlled deflector was made (Fig. 5a, b and c) through which a flexible forceps can be introduced and bent into position and further advanced towards the periphery. The same mechanism can be employed to direct a cytology brush or a radio-opaque catheter into the periphery for suction or brush cytology.

THE FLEXIBLE ENDOSCOPES

In 1930 Lamm reported that an image can be transmitted through flexible fiber glass threads.[11] In 1954 Hopkins described the first flexible fiber coherent image bundle recommended for endoscopy.[12] Hirschowitz et al employed it clinically in the gastrointestinal tract, in 1958.[13] Ikeda et al pioneered in the bronchial tree.[14] The basic principle is depicted in Figure 6.

Flexible Laryngoscope. The flexible laryngoscope is essentially a slightly modified bronchoscope which can be introduced transnasally. I have found that the transnasal introduction of the flexible scope is much more time consuming and unpleasant for the patient than the introduction of the indirect laryngoscope. The maneuvering, flexing of the tip and rotation, needs more endoscopic skill and coordination than the rigid one. The capital outlay of the flexible one is significantly more. There are applications in cases where correc-

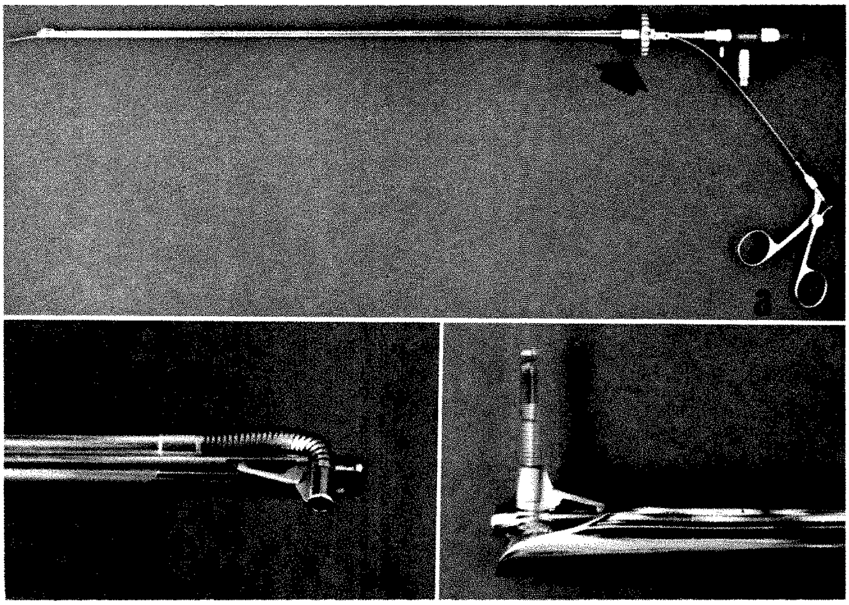

Fig. 5. Lateral telescope with biopsy forceps deflector. For upper lobe lesions. a) Turning the wheel (arrow) of the bending mechanism at the working end will flex the forceps into view. b) Close-up from working end with bending mechanism. c) Forceps can be advanced into the periphery and accurate tissue samples obtained.

tive surgical procedures are required, e.g., cleft palate, in which film records, audio and visual, of speech performance in the pre- and posoperative period are needed. This technique can be of great help for speech defects where the observation of coherent speech is of importance. For the anesthesiologist it can be of help in a small group of obese patients, with short necks or other anatomical anomalies, where direct intubation is extremely difficult.

When it comes to fine details, good contrast, and natural color reproduction, which is so important to recognize inflammation or small organic lesions, the rigid scope is the method of choice. In case of functional disorders, even in the presence of an inserted rigid scope, the patient can phonate sufficiently to discover slight impairments of function.

In general, the image quality of a rigid rod-lens system today is greatly superior to any available flexible fiber ones.[15]*

Flexible Fiber Bronchoscope. The great attraction is that it can be introduced more easily than an open tube because of the smaller size and flexibility and can be advanced further into the periphery. Ikeda started first with small scopes (4 mm) which were used for visualization only, but soon it became larger in O.D. to accommodate the remote tip control and the biopsy channel for tissue sampling.

In a large number of cases peripheral lesions are even out of the visible range for the flexible fiber scope. The scope is used to direct the biopsy forceps into the appropriate orifice and advance the tissue sampling device (biopsy forceps or brush) into the periphery towards the lesion, using *fluoroscopic guidance.* (Fig. 7). The flexible fiber bronchoscope is an extremely delicate and costly instrument which needs good care and maintenance. The tip can be remote controlled, but only in one plane, or up and down. Two planes (four-way control) could not be incorporated because of the small outside diameter.

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*A 16 mm filmstrip was projected displaying the same patients' lesions taken through a rigid indirect laryngoscope versus the flexible one.

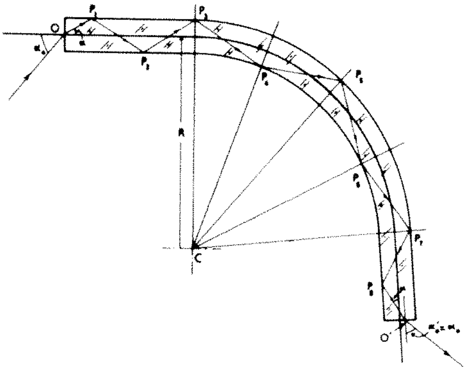

Fig. 6. Schematic diagram of a light (ray) passage through a bent flexible fiber glass thread due to internal reflection. Diameters of threads: 12-20μ. Several thousand threads are packaged in a bundle. If both ends are precisely assorted, an image can be transmitted. This is the basic principle of function of the coherent image bundle of a flexible fiber endoscope. (From: Hopkins HH: Physics of the fibreoptic endoscope, in Berci G (ed): *Endoscopy*. Courtesy: Appleton-Century-Crofts, New York, 1976.)

Therefore, some additional movement such as rotation (torque) has to be applied which results in increased breakage of the fibers.[16]

There has been a recent trend to increase the diameter of the biopsy channel, but to accomplish this the other compartments, i.e., the image bundle must be decreased. The fiber bundles consist of several thousand individual fiber threads with a "dead interspace." If the number of fibers are smaller, this "chicken wire phenomenon" appears more emphasized and can be disturbing (Figs. 8 and 9).

The major problem is the rigid part of the biopsy forceps itself, which cannot be shortened and therefore requires a certain larger bending radius to facilitate advancement (Fig. 10). It is most disconcerting if the operator is in a proper position in one of the upper lobes, in a hyperflexed position discovering a lesion, and the biopsy forceps cannot be advanced. The scope has to be straightened out first (Fig. 11) to permit the insertion of the biopsy forceps and reposition. The recent trend to increase the diameter of the biopsy channel by a few tenths of a millimeter does not help to solve this problem. We have not gained very much in easing biopsy manipulation nor the ability to obtain larger tissue samples because the size of the forceps remains the same, but the image quality is significantly sacrificed. In addition, the viewing angle of the recent models is made narrower and therefore orientation is more difficult.

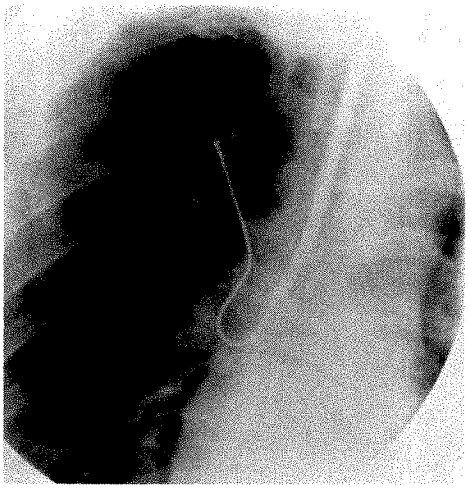

Fig. 7. X-ray film of flexible fiberscope with a biopsy forceps advanced towards a peripheral target. These lesions are out of vision, even for the fiberscope. The appropriate orifice is visualized and the forceps advanced toward the suspected area *under fluoroscopic guidance.*

Flexible fiber bronchoscopy became very popular. It can be easier introduced than an open tube. The indications are broader. It became a valuable tool in the intensive care unit, in peripheral lesions with multiple biopsies and/or selective cytology sampling, etc. This does not mean that an open tube with a telescope, optical biopsy forceps became a museum piece. Our training programs should include every endoscopic technique which can be useful as a diagnostic aid. I would rather emphasize that a good endoscopist must have the capability to select cases and corresponding technique, to perform any endoscopic procedure in the upper respiratory tract with skill.

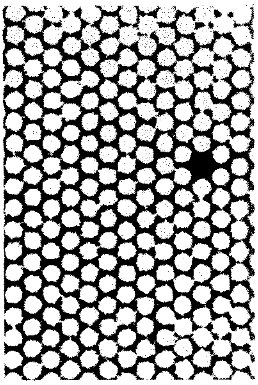

Fig. 8. Enlarged view of the pattern of a coherent fiber image bundle. The single black dot represents one broken fiber. The interspace between the individual fiber threads does not transmit an image (dead space). If more fibers are packaged in a bundle, the image appears smoother. If the bundle diameter is decreased, this "chicken wire phenomenon" pattern will be coarser and will disturb the view.

MINIATURE ENDOSCOPES

Pediatric Bronchoesophagology. This area profited most from the introduction of the Hopkins-Storz rod-lens system.[17] Despite miniaturization, the image quality obtained through this small size telescope is remarkable compared with the pinpoint view obtained looking through the small, open, pediatric tubes (Fig. 12).

Figure 13 displays a new universal bronchoscope which is available in a length of 26 cm and sizes of 3, 3.5 and 4.0. A miniature telescope with a crisp, wide-angle display can be introduced and advanced beyond the sheath if required.

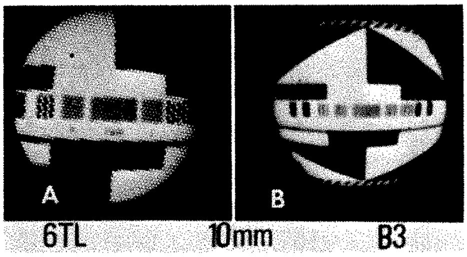

Fig. 9. Resolution test pattern, as seen under identical condition (10 mm object distance). A) Machida 6 TL type bronchoscope with smaller bundle, narrower viewing angle, and biopsy channel slightly enlarged. B) Olympus Type B3, larger viewing angle and image bundle, and biopsy channel slightly smaller.

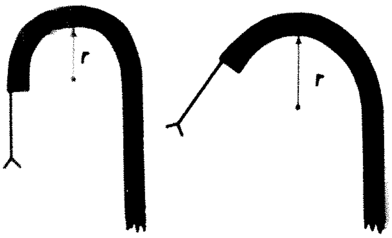

Fig. 10. The rigid part of the small flexible biopsy forceps determines the bending radius. A short radius would be ideal so that the forceps still could be advanced in a flexed position without difficulties. Unfortunately, this is not the case, even in those scopes which are provided with a larger channel (see Fig. 11).

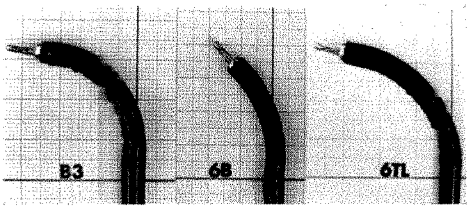

Fig. 11. Left to right, Olympus Type B3 (larger image bundle and smaller channel), Olympus Type 6B (larger channel and smaller image bundle), Machida 6 TL (larger channel and smaller image bundle). *Maximum* bending radius is displayed through which the biopsy forceps still can be advanced.

Foreign Body Removal. One of the greatest achievements with this instrument is the more accurate and easier removal of foreign bodies under direct visual control. As mentioned above (adult bronchoscopy section) if the

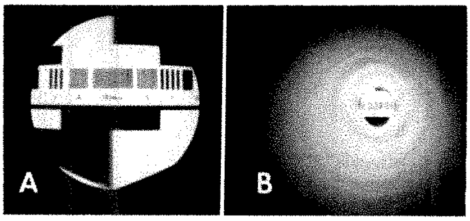

Fig. 12. Comparison of A) Miniature telescope inserted, with B) Resolution test pattern as seen through a pediatric open tube bronchoscope (size 3.5).

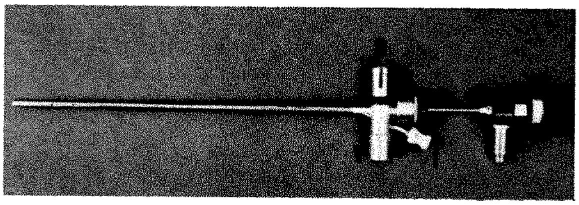

Fig. 13. Pediatric bronchoscope, length 26 cm. Sizes: 3, 3.5 and 4.0. A miniature telescope can be introduced through a rubber seal. p - Prismatic light deflector. v - Connection to assisted ventilation. i - Instrument channel.

foreign body or lesion is seen and the forceps introduced, we aim, but the forceps itself obscures the vision in the most crucial moment. The actual manipulation is performed *semiblindly*. This problem is much more emphasized in pediatrics where the size of the sheath or the lumen is much smaller. A miniature alligator forceps is available which can be advanced through the instrument channel beside a telescope into the bronchial tree (Fig. 14).

It is very important to minimize the number of manipulations and try to succeed with the first attempt. If it has to be repeated, this results in immediate oozing, hypersecretion and extension of the procedure. The general principles of foreign body removal are precision and speed. They can be enhanced by using the optical forceps technique.

For soft foreign bodies an optical peanut forceps was made which is built together with a telescope. The basic principle is the same, namely, to control the grasping or manipulating action under vision.*

Another improvement is the double illumination system. As an open tube, a prismatic deflector is inserted proximally (Fig. 14). In case of fogging or a dirty lens, the telescope is withdrawn and the prismatic deflector forwarded, providing immediate illumination. In other words, we are never left in the dark during suction or manipulation. A double illumination system is a safeguard.

The esophagoscope is similar, in essence, to the bronchoscope. The tip of the sheath is flared to facilitate better

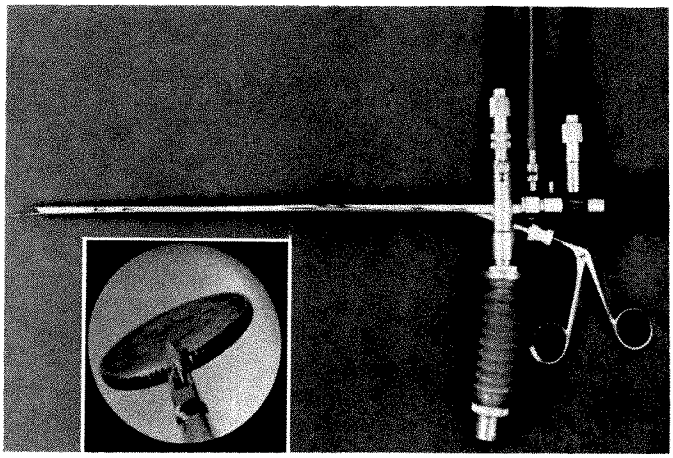

Fig. 14. Assembled pediatric bronchoscope with telescope. Alligator foreign body forceps inserted. v - Flexible connector to assisted ventilation. p - Proximal prismatic light deflector in parking position. fo - Fiber optic cable of telescope illumination. a - Antifog. Insert) Telescopic view. Alligator forceps grasping a coin (dime).

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*At this stage a 16 mm movie filmstrip of the bronchial tree of a newborn with a tracheo-esophageal fistula was shown and a foreign body removal was demonstrated.

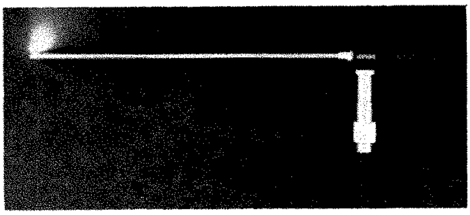

Fig. 15. Retrolaryngoscope. Diameter: 4 mm including fiber optic light transmission. Direction of (retrograde) view 120°.

exploration of the esophagus. The ventilation outlet is omitted, but all the accessories, including the telescope, are interchangeable with the bronchoscope set.

Retrolaryngoscopy. A 4 mm telescope (including a fiber light transmission) with 120° retrograde view allows us to inspect the subglottic space through a tracheostomy, to evaluate the extent of a lesion, assess edema, or inspect the vocal cord conditions from below. Turning this telescope 180° the trachea can be visualized to the bifurcation and the reaction to the tracheostomy tube evaluated (Fig. 15).*

CONCLUSION

A huge number of broncho-esophago-laryngo- endoscopic examinations are performed in the adult and children per year. Despite these facts basic research activities are seldom found in the literature. Our goal was to change the previous tunnel vision or keyhole appearance to a panoramic view. The possibility of obtaining a permanent film record with the ability to analyze motion, explained previously unknown phenomena. To insert a print into the patient's chart supports significantly our description however accurate. Film documentation is of immense help in teaching endoscopic findings and technique.

I do hope that our research activities in this field will trigger and further propagate these projects to achieve our final goal: improved patient care.

I would like to recall a quotation from Dr. Jackson's autobiography: "Be sure you are right and then look to see what is wrong. Be sure you are right, but not too sure."[18] In our research activities during the past 20 years, we have not forgotten his remarks.

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*A 16 mm movie film strip was shown taken through this retrolaryngoscope.

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The rigid endoscopes employed in this study were manufactured by Karl Storz Endoscopy Company, Tuttlingen, W. Germany and distributed by Karl Storz Endoscopy America, Inc., Los Angeles, CA. The flexible fiber bronchoscopes used were distributed by Olympus Company of America, New Hyde Park, NY and Machida America, Inc., Closter, NY.

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GUIDELINES OF GRANTS
TRUSTEES OF AMERICAN OTOLOGIC SOCIETY

A matter of continual concern to the members of the Board of Trustees of the American Otological Society is the determination of guidelines for the making of grants from its research fund. The following is our current formulation of policy.

Our objective is clearly before us as the problem of otosclerosis: its diagnosis and management, the possible causes and underlying conditions (such as the hereditary background), and an understanding of the disorder that may lead eventually to its prevention and cure.

Our present lack of understanding of the disorder and the absence, as far as known, of any similar condition in animals below man, make research in this field particularly difficult. A dirrect attack on the disease is hardly feasible; therefore it seems to be sound strategy to try circuitous approaches, such as the investigation of bone development, growth, and repair under various conditions, and the study of other diseases that show suggestive correspondence. It is possible that directions of investigation that may seem initially somewhat remote from otosclerosis itself may provide insights that will eventually lead to success in reaching our goal. The applicant should describe correlations between proposed research with the clinical pathological entity of otosclerosis.

Therefore, our policy is to aid and encourage research in the immediate field of otosclerosis and also in adjoining fields if in our considered opinion there is a substantial promise that the results obtained will be of assistance in the ways just indicated, and may lead to the attainment of our objective.

To stimulate the attainment of this objective, the Board of Trustees wishes to remind the general otolaryngologic community that funds are still available for suitable grants. Application forms may be obtained from the office of the secretary of the Research Fund Trustees of the American Otologic Society.

The grant request should be submitted by January 31, 1979, to David A. Hilding, MD, Secretary, 1300 Tower Road, Winnetka, IL 60093. Telephone (312) 441-5023.

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EPIGLOTTITIS

TWENTY-YEAR STUDY WITH TRACHEOTOMY

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One hundred and seventy patients with acute epiglottitis were admitted to the Childrens Hospital of Los Angeles between the years 1957 to 1977. No deaths occurred in any of these patients, all of whom were treated with tracheotomy to support and ensure the airway. The records of 147 of these patients were available for review. No serious complications occurred from tracheotomy in any of the patients in this study. Tracheotomy is a safe method for caring for the airway problem in epiglottitis in a setting such as is available at the Childrens Hospital of Los Angeles. The median range of total days with tracheotomy was five to six days, and the median range for total days of hospitalization was six to seven days. Complications were never severe and in the extreme, merely prolonged hospitalization by a few days. This highly lethal disease is curable with antibiotics and an artificial airway, and it is questionable whether conservative medical measures with observation should be acceptable. The establishment of an airway, whether by tracheotomy or endotracheal intubation, is mandatory in the treatment of this disease.

Epiglottitis is a disease with sudden onset leading to rapid, progressive, severe obstruction of the airway within a matter of hours. It is much more common in children than adults. Recent reports stress the effectiveness of endotracheal intubation in the treatment of the airway obstruction which occurs in this disease. This paper reports the statistical analysis of a series of children with epiglottitis treated with tracheotomy. None of the patients in this study were intubated or bronchoscoped, except for the establishment of an airway in order to do an elective tracheotomy.

This retrospective study reviews all the available charts of patients with acute epiglottitis treated by tracheotomy, for the control of airway obstruction, at the Childrens Hospital of Los Angeles over the past 20 years. The study will discuss the clinical findings, effectiveness and complications of tracheotomy as the definitive form of treatment to establish and maintain the airway. Unfortunately, no statistics were available during the period of this study with respect to the number of children who were treated conservatively, nor those who died because of failure to diagnose the disease. The analysis does not cover any of those children for whom the Division of Otolaryngology was not consulted for therapy.

The medical personnel involved in the treatment of this disease included the pediatrician who usually first saw the child, the otolaryngologist who performed the tracheotomy and the anesthesiologist who administered the anesthesia for the surgical procedure.

HISTORICAL REVIEW

Theisen[1] in 1900 reported three cases of a condition referred to as "angina epiglottidea." Sinclair[2] in 1941 first described a form of laryngitis due to *Hemophilus influenza* type B. Lemierre et al,[3] in 1936 isolated *H. influenza* as a cause of severe laryngeal edema and obstruction. Epiglottitis or supraglottic laryngitis became popularized as a clinical entity with subsequent papers by Miller[4] in 1948, Berenberg and Kevy[5] in 1958, and Poole and Altman[6] in 1963. These papers were im-

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Presented at the meeting of the American Broncho-Esophagological Association, Palm Beach, Florida, April 24-25, 1978.

portant in arousing the clinicians' awareness of this serious and potentially fatal disease.

An important literature review and update of the comparative results using the three different modalities of airway protection, intubation, tracheotomy and close observation, was made by Cantrell et al,[7] who reviewed 740 cases. Of these, 348 (46.5%) were tracheotomized, 216 (28.8%) were intubated and 214 (24.7%) were observed. The highest mortality rate (6.1%) was in the group treated by observation. Mortality rates in the intubated and tracheotomized patients were 0.86% in the latter, and 0.92% in the former.

Benjamin and O'Reilly[8] point out that, "Occasional good results with treatment with IPPB, steroids, antibiotics and fluids with observation should not delude physicians in this unpredictable disease with the use of unpredictable modalities." They stress that severe toxemia and prostration are due to septicemia and that respiratory and cardiac arrest, once established, are associated with high mortality and rare recovery.

CLINICAL FEATURES

Basically, the picture of acute epiglottitis includes the following symptoms in a previously healthy child, usually between the ages of one to five years: sudden onset of fever, severe sore throat and dysphagia, with drooling and increasing airway obstruction rapidly progressing to overwhelming toxemia and prostration (Fig. 1).

The clinical pictures of epiglottitis and subglottic laryngeal infection usually differ significantly in their presentations. In the latter, the onset is slow, with antecedent upper respiratory infection accompanied by hoarseness and a barking seal-like cough. Dysphagia is absent unless accompanied by other complications in the throat or deep neck. Stridor is of a crowing type, and very little fever or cervical lymphadenopathy is present. In epiglottitis, the child prefers to sit up, drools, cannot swallow without severe pain or choking, and has a fluttering stridor with muffled or full voice (Fig. 1). There is usually extensive cervical adenopathy, high fever, and the voice is rarely hoarse. Unlike subglottic laryngeal infection, the child with epiglottitis becomes progressively more anxious, toxic, prostrate, air hungry and may suddenly die if an airway is not established.

BACTERIOLOGY

The most frequent causative organism producing supraglottic laryngitis is *H. influenza* type B, a Gram negative encapsulated bacillus. Positive cultures are most likely obtained from the larynx or tracheobronchial tree secretions. Turk and May[9] in 1967 showed that blood samples from infants under three months of age had a bacteriocidal effect on an encapsulated strain of *H. influenza.* This bacteriocidal effect was absent in the blood of children three months to three years of age. They concluded that passive immunity to *H. influenza* type B acquired from the mother was lost in the first three months of age and active immunization was restored by nature in most cases at three years of age or later. This fact may account for the high incidence of epiglottitis in this early age group.

DIAGNOSIS

The diagnosis may be made chiefly on the basis of the clinical picture. An acute onset of the previously described clinical features should arouse suspicion of epiglottitis on the part of the physician. Careless attempts at visualizing the epiglottis with tongue blades or other instruments outside of the carefully controlled situation in an operating room should be discouraged, since sudden irreversible airway obstruction may occur. A cooperative child may, at times, protrude the tongue sufficiently to allow visualization of the typical cherry red swollen epiglottis (Fig. 2). While lateral x-rays of the neck may show the swollen laryngeal structures, this type of examination should be discouraged as it causes unnecessary delay and increases potential risk to the already compromised airway. The child suspected of having epiglot-

TABLE 1. DURATION OF ILLNESS PRIOR TO TRACHEOTOMY

Hours	*No. of Patients*
0.6	32
6-12	71
12-24	35
24-48	3
48	1
Unknown	4

titis should be taken to an operating room where airway insurance can be established, by either intubation or a tracheotomy, with a maximum of efficiency and a minimum of danger to the patient.

METHODS AND MATERIALS

The medical records of 147 pediatric patients who required tracheotomy for epiglottitis at the Childrens Hospital of Los Angeles, between the years 1957 through 1977, were reviewed.

This retrospective study was designed to investigate those patients who required tracheotomy for epiglottitis. Consequently, those patients who received medical therapy exclusively or those who expired prior to reaching the operating room were not included in this study. Medical therapy is defined as the treatment used for those cases who required no surgical procedure and, therefore, were treated conservatively. The records of these patients were not available for study. The total number of patients who did not require tracheotomy for epiglottitis is not known. It should be noted that patients with this disease were rarely treated without surgery at this institution. Once diagnosed, the children were immediately taken to the operating room for a tracheotomy.

All patients in this study were carefully evaluated and managed by both the pediatric and otolaryngological staff of the hospital. The anesthesiologists were involved only in the surgical procedure.

TABLE 2. SYMPTOMS

	No. of Patients
Inspiratory stridor	107
Subcostal retractions	84
Lethargy	32
Adenopathy	29
Cyanosis	18
Difficulty swallowing, drooling	17
Respiratory distress	15
Croupy cough	9

The total number of patients who required tracheotomy for supraglottic laryngitis during the study period was 170. Twenty-three charts were not found and, therefore, are not included in this study. A mortality review showed no deaths occurred in the total number of 170 tracheotomized patients.

Frequently the emergent nature of this disease precluded an opportunity for adequate recording of the history and physical examination, and performance of appropriate laboratory tests. Emphasis was placed on getting the patient to an operating room for the establishment of the airway. Many charts, therefore, were grossly lacking in the information required for this study. The oldest charts were found to be most lacking in the necessary data.

RESULTS

The acute onset of epiglottitis is nowhere better exemplified than the duration of illness prior to tracheotomy (Table 1). One hundred three out of 147, or 70% of the patients, presented to the hospital less than 12 hours after the onset of symptoms. More than 94% of the patients presented less than 24 hours after onset of symptoms. The one patient who became ill five days prior to tracheotomy had chronic leukopenia of unknown etiology. The duration of symptoms was not found in 4 of the 147 case histories.

The most common symptoms were stridor, airway obstruction with retractions, lethargy and dysphagia (Table 2). There were 15 patients who had only the description of "respiratory distress" in their medical records.

The majority of the patients were afebrile within 24 hours after tracheotomy (Table 3). Those who remained febrile after 24 hours had complicating factors such as meningitis, pneumonia and diarrhea.

The age of the patients ranged from nine months to 16 years (Table 4). The

TABLE 3. DURATION OF POSTOPERATIVE FEVER

Hours	*No. of Patients*
0-12	39
13-24	43
48-72	29
72	4

TABLE 4. INCIDENCE OF EPIGLOTTITIS ACCORDING TO AGE AND SEX

Age	*Sex*
0-11 mo — 1	M 85
12-23 mo — 20	F 62
2 years — 37	
3 years — 24	
4 years — 29	
5 years — 13	
6 years — 12	
7 years — 1	
8 years — 5	
9 years — 2	
12 years — 1	
13 years — 1	
16 years — 1	

Mean: 3.5 Yr
Median: 2-3 Yr

mean was 3.5 years and the median was between two and three years. Approximately 75% of all the patients were four years or younger. These data were also consistent with those of previous studies.[5,10]

There was definitely a larger number of male patients in this study (Table 4). It is interesting that a study of endoscopy in the neonate from this hospital showed that the male more frequently required tracheotomy with no data to explain this difference.[11] Baxter[10] in 1967 found no real difference in number between male and female patients, whereas Berenberg and Kevy[5] in 1958 reported a definite male predominance.

The number of patients from year to year was quite variable (Table 5). They ranged from a low of 2 in 1969 to a high of 14 in 1958. The variability did not follow a specific pattern. The introduction of ampicillin or chloramphenicol (during the late 1950s and early 1960s) seemed to have had no effect on the yearly incidence of this disease. The average yearly incidence of eight is consistent with those of previous studies.[5,10]

TABLE 5. INCIDENCE — YEAR

1957 - 11	1964 - 6	1971 - 8
1958 - 14	1965 - 5	1972 - 6
1959 - 13	1966 - 7	1973 - 4
1960 - 7	1967 - 8	1974 - 8
1961 - 3	1968 - 5	1975 - 9
1962 - 4	1969 - 2	1976 - 5
1963 - 6	1970 - 6	1977 - 10

TABLE 6. INCIDENCE — MONTH

Jan - 11	Jul - 18
Feb - 8	Aug - 14
Mar - 16	Sep - 2
Apr - 15	Oct - 9
May - 11	Nov - 17
Jun - 11	Dec - 15

The monthly incidence (Table 6) is unlike the findings of previous retrospective studies which noted increased numbers during the winter months.[5,10] No specific season of the year predominated in this geographic area. In this study, most patients were admitted in July, November and March. The least number of patients was seen in September, February and October.

The laboratory data was consistent with those of previous studies.[5] The leukocyte count was greater than 16,000 (and a definite "left shift" was seen) in most of the patients (Table 7). The most common organism cultured from the blood and the tracheobronchial tree was *H. influenza* type B (Table 7). Sixty-three percent of the cultures of the tracheobronchial tree and approximately 57% of the blood cultures grew this organism.

Ampicillin and chloramphenicol were the most common antibiotics utilized. Table 8 illustrates the spectrum of antibiotics used.

The mortality rate was zero for the 147 patients who required tracheotomy for epiglottitis (Table 9). No deaths are recorded among the total of 170 patients.

Complications occurred in 28 patients (Table 9). Thirteen of the 28 patients had one of the following noted on routine postoperative examination: subcutaneous emphysema, pneumothorax and pneumomediastinum. Twelve of these 13 patients required no intervention and the problems resolved spon-

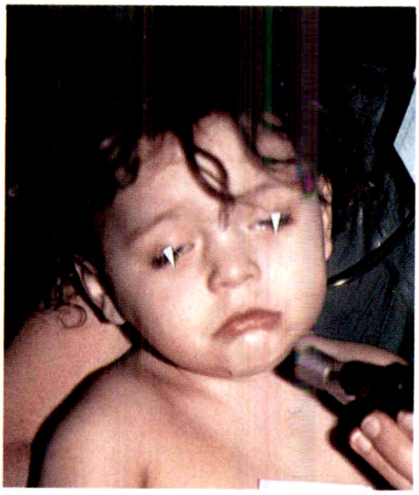

Fig. 1. Child sitting up, drooling, with severe overwhelming toxemia, appears dyspneic and is prostrate.

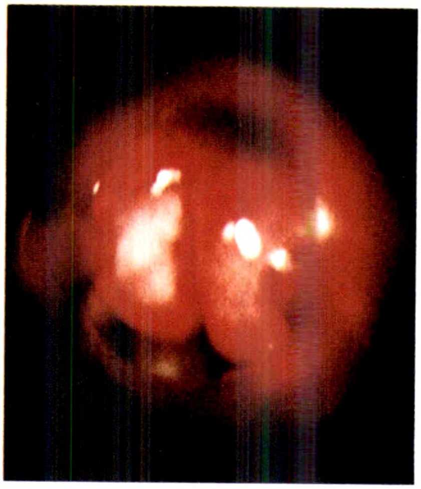

Fig. 2. Photograph of the larynx showing very edematous epiglottis and aryepiglottic folds. The cleft on the laryngeal surface seen in many cases is a guide for passing a bronchoscope or for intubation.

TABLE 7. LABORATORY DATA

Total leukocyte count	
Less than 10,000	9
10,000 to 15,000	28
16,000 to 20,000	35
21,000 to 25,000	24
26,000 and greater	34
No blood drawn	17
Blood culture	
None	98
H. influenza (B)	28
No growth	18
H. influenza (not A or B)	1
Cultures from larynx and tracheobronchial tree	
H. influenza (B)	83
(β lactamase +)	1
Streptococcus (B)	27
S. aureus	22
N. catarrhalis	16
H. influenza (not A or B)	6
P. aeruginosa	5
Micrococcus	5
S. pneumoniae	3
None obtained	16
No growth	3
Other	10

taneously. One patient, a 16-year-old male, required a chest tube for approximately 24 hours, was decannulated on the fifth postoperative day, and discharged without further complications on the sixth postoperative day.

Of the remaining 15 patients, 6 had problems with increased secretions and poor tolerance of plugging of the tracheotomy tube, thus causing delay in decannulation. Five patients had bleeding postoperatively, two of which required surgical intervention, and in the other three the bleeding stopped spontaneously. The remaining four patients had granuloma, subglottic bar, mild tracheal stenosis and tracheal tube dislodgement. All were decannulated without difficulty and were normal on follow-up examinations.

TABLE 8. ANTIBIOTICS UTILIZED

Ampicillin	78	Gantrisin®	3
Chloramphenicol	60	Achromycin®	10
Polymixin	2	Streptomycin	21
Keflin®	2	Sulfadiazine	5
Penicillin	28	Dicrysticin®	1
Crysticillin®	2	Tetracycline	2
Erythromycin	2	Terramycin®	1
Triple Sulfa®	2	Oleandromycin	1

TABLE 9. MORTALITY AND COMPLICATIONS

Mortality	— 0	
Complications	— 28	
Pneumothorax		13/28
Pneumomediastinum		
Subcutaneous emphysema		
Excessive bleeding		5/28
Granulomas		10/28
Subglottic bar		
Tracheal stenosis		
Tracheal tube dislodged		
Excessive secretions		

The 12 patients who had clinically insignificant extravasation of air postoperatively are not considered in the complication rate. The more realistic complication rate was 10%. In no instance was the life of the patient compromised or a postoperative morbidity incurred. In the extreme, they produced a somewhat prolonged hospitalization.

The duration of hospitalization ranged from four days to three months and 26 days (Table 10). More than 90% of the patients were discharged by the ninth postoperative day and approximately 81% of the patients were discharged by the seventh postoperative day. If one excludes the longest hos-

TABLE 10. TOTAL DAYS HOSPITALIZED

Days	*No.*	*Days*	*No.*
4	3	12	3
5	21	14	1
6	38	15	2
7	28	17	1
8	29	18	1
9	7	21	1
10	8	23	1
11	2	115	1

Mean 7.5 days.
Median 6-7 days.
Range 4 days to 3 mo and 26 days.

TABLE 11. TOTAL DAYS WITH TRACHEOTOMY

Days	*No.*	*Days*	*No.*
3	6	9	3
4	32	10	2
5	37	12	1
6	25	14	1
7	23	16	2
8	13	20	1
		113	1

Mean 6.3 days.
Median 5-6 days.
Range 3-3 mo, 22 days.

pitalized patient (a 17-month-old patient with cystic fibrosis), the mean would be 7.5 days and the median would be between six and seven days. The delay in decannulation of the 17-month-old child with cystic fibrosis was unquestionably due to the systemic disease. This patient was decannulated approximately two days prior to discharge, at which time the larynx and subglottic space were noted to be perfectly normal. Thirteen patients remained in the hospital more than ten days. Of these 13, 8 patients had problems with decannulation. The other five patients had the following: cystic fibrosis, bacterial meningitis, diarrhea, chronic leukopenia of unknown etiology, and febrile seizure. It is interesting to note that the four patients who remained for the longest duration were seen and treated in 1957, the year that this study began.

The total number of days with a tracheotomy tube in the study ranged from three days to three months and 22 days (Table 11). Approximately 92% of the tracheotomy tubes were removed by the seventh postoperative day. The eight patients previously mentioned with problems of decannulation had the following: one patient had subglottic granuloma, another had mild tracheal stenosis, and six who had excessive secretions were found to be normal at endoscopic examination and subsequently decannulated without problems.

CONCLUSIONS

Tracheotomy is a safe and dependable method for treating airway obstruction in patients with acute epiglottitis. Of the 170 patients admitted to the Childrens Hospital of Los Angeles between 1957 and 1977, there were no deaths. The medical records of 147 patients who required tracheotomy were reviewed in detail. No serious complication occurred from tracheotomy in any of the patients in this study. Tracheotomy, therefore, in a setting such as is available in the Childrens Hospital of Los Angeles, is a safe method for caring for the airway problems in this disease. While in some centers there may be some disagreement regarding whether tracheotomy or endotracheal intubation should be used in the treatment of this disease, there is no question that the establishment of an airway is mandatory. While a 10% complication rate found in this series would appear to be high, none of the complications were severe, and in the extreme, merely prolonged hospitalization by a few days. This highly lethal disease is curable with antibiotics and an airway, and it would seem questionable whether any conservative medical measures with observation should be acceptable. Insurance of the airway is tantamount to cure.

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NINCDS NOTES*

NINCDS BUDGET NEARING COMPLETION

The NINCDS FY 1979 budget will be larger than last year's, but the amount of the increase remains to be determined. The final figure hinges on two Congressional actions: first, a compromise must be reached between the House recommendation of $188.9 million (not including training funds) and the Senate's recommendation of $225 million (exclusive of training funds); and second, final passage of the Department of Health, Education, and Welfare's (DHEW) appropriation must await Congressional resolution over an amendment tacked on regarding federal funding for abortions.

Approximately $8 million in training funds will be added to the final budget, which is scheduled to go into effect October 1. If a prolonged debate over the abortion issue holds up passage of the DHEW appropriations bill, the Institute would operate under a continuing resolution (using resources based on the FY 1978 budget allocation) until the bill is passed.

Institute Director Dr. Donald B. Tower says, "The proposed sizeable increase in the NINCDS budget should enable us to fund research at a more appropriate level than has been possible in previous years. In large part, the House and Senate Subcommittee's proposed increase reflects the successful efforts of voluntary and professional organizations in emphasizing to Congress the importance of research on neurological and communicative sciences and disorders.

RESEARCH GRANT AND TRAINING AWARDS

The NINCDS advisory council at its May 25-26 meeting recommended funding of 153 research grants at $9.5 million. The council also recommended funding of 16 Research Career Development Awards (all to PhDs); 11 Teacher Investigator Development Awards (4 to PhDs and 7 to MDs); and 97 Individual National Research Service Awards. Of the latter awards, 82 recipients are PhDs, 10 are MDs, 1 is an MD/PhD, and 4 are listed in the "other" category. No Institutional National Research Service Awards were reviewed; applications for these awards are considered only at the council's January meeting.

K. KENNETH HISAOKA DIES

Dr. K. Kenneth Hisaoka, the Institute's Extramural Activities Program Director for the past year, died May 26 of cancer at the NIH Clinical Center. Dr. Hisaoka had coordinated the administration of the Institute's Extramural Activities Program.

Currently, Dr. J. Buckminster Ranney will function as the Acting Director. The NINCDS will begin seeking candidates for the job.

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*This column is prepared monthly by the Office of Scientific and Health Reports, National Institute of Neurological and Communicative Disorders and Stroke. For further information, write or call Carolyn Holstein, NINCDS/OSHR, NIH Bldg. 31, Room 8A-16, Bethesda, MD 20014. (301) 496-5751.

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SPUTUM CYTOLOGIC DIAGNOSIS OF UPPER RESPIRATORY TRACT CANCER

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Lewis B. Woolner, MD
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Sputum cytologic testing has been applied in the screening of high-risk individuals for presymptomatic lung cancer. This same screening procedure sometimes identifies patients with upper respiratory tract cancers and thereby may permit earlier treatment. Patients enrolled in the Mayo Lung Project undergo sputum cytologic and chest roentgenographic screening at four-month intervals and are compared with matched controls who are not intensively screened. Experience to date indicates an incidence rate of approximately 1 per 1,000 per year of cancer in the upper respiratory and alimentary passages among males more than 45 years old who are heavy cigarette smokers. This compares with a rate of approximately 4 per 1,000 per year of lung cancer. Recognition of early cancer of the upper respiratory tract is an additional benefit of screening for lung cancer. Since cigarette smoking represents an etiologic agent common to both upper and lower respiratory tract cancers, tumors should be searched for in both sites in this high-risk population.

The Mayo Lung Project was initiated in 1971 as a program for assessing the feasibility of screening subjects at high risk for bronchogenic carcinoma.[1,2] The goal was to determine whether the survival rate was significantly greater among screened patients in whom lung cancer developed compared with the rate in control subjects not similarly screened. The National Cancer Institute sponsored similar, although not identical, programs at Johns Hopkins University and Memorial Sloan-Kettering Cancer Center.[3] Several patients with tumors in the upper respiratory and alimentary passages have been encountered in the course of the Mayo Lung Project study and these form the basis of this report.

METHODS AND MATERIALS

Eleven thousand patients were interviewed. They were selected because they were at high risk for the development of respiratory tract cancer. These were males more than 45 years old who were smoking one package of cigarettes or more daily or had done so within the preceding year. Nearly all had smoked heavily for more than 20 years. All patients had an initial physical examination, including a standard 35.6 by 43.2 cm chest roentgenogram and a cytologic test on three-day pooled sputum. Those who were found to have cancer of the respiratory tract on this examination (prevalence cases) were appropriately treated and were excluded from subsequent incidence data. Also excluded were patients who did not complete the initial screening and those with serious illness that was thought to preclude participation in a long-term prospective study. The remaining 9,218 patients were randomized into a *participant* group, who had repeat screening every four months by means of posteroanterior and lateral chest roentgenograms, a sputum cytologic test, and a lung health questionnaire, and a *control* group, who were not rescreened. The control subjects are contacted once a year, and detailed records of their health care, if any, are maintained.

Cytologic Diagnosis. The specimens for sputum cytologic study in each patient are pooled, three-morning collections of spontaneous deep-cough sputum fixed in 50% alcohol and 2% Carbowax®[4] (Doac Pharmacology Company, Inc., Westbury, Long Island, NY).

Carcinoma of the upper airway is generally of the squamous cell type. Cytologic diagnosis of squamous cell cancer is based on conventional cellular criteria of malignancy. The features vary somewhat from case to case but generally include increase in size of the cells and nuclei, variation in size and shape of cells and nuclei, abnormal nuclear-cytoplasmic ratio, nuclear hyperchromasia with coarse chro-

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From the Mayo Clinic and Mayo Foundation, Rochester, Minnesota. This investigation was supported in part by Research Grant CB-53886 from the National Institutes of Health, Public Health Service.

Presented at the meeting of the American Broncho-Esophagological Association, Palm Beach, Florida, April 24-25, 1978.

TABLE 1. NUMBER OF MAYO LUNG PROJECT PARTICIPANTS AND CONTROLS WITH CANCER IN THE UPPER AIRWAY OR LUNG THROUGH MARCH 1, 1978

	Participants	*Controls*
Total no. entered	4,622	4,596
No. with upper airway cancer	18*	19
No. per 1,000 persons/yr	1.17	1.19
No. with lung cancer	68*	42
No. per 1,000 persons/yr	4.28	2.76

*One patient with airway cancer had adenocarcinoma of lung subsequently.

matin pattern, and a wrinkled or irregular nuclear membrane. Lesser degrees of cellular change are designated squamous cell "atypia" and are generally graded as slight, moderate, or marked in degree. Evidence of squamous differentiation in atypical or frankly carcinomatous cells is provided by the presence of intracytoplasmic keratin, which imparts a glassy or homogeneous quality to the cytoplasm and is readily detected by a brilliant orange coloration with the Papanicolaou stain.

Carcinoma of the upper respiratory tract which develops on the basis of a preexisting atypical leukoplakia can be expected to shed clumps or sheets of cells that are more highly keratinized than those that arise from the usual, less highly keratinized in situ squamous cell carcinoma. Although some carcinomas of the upper respiratory tract are thus somewhat distinctive on cytologic presentation, it is in general not possible to distinguish cytologically between a squamous cell carcinoma arising in the upper portion from that developing in the lower portion of the respiratory tract.

Examination. When a patient with positive sputum cytologic findings and a normal chest roentgenogram has been identified, preparation is made for bronchoscopy.[5,6] However, as part of the prebronchoscopy evaluation, a complete otorhinolaryngologic examination is carried out in the office in search of tumors in the upper respiratory and alimentary passages. The diagnosis of cancer in the upper respiratory or alimentary tract is established by biopsy — performed either in the office or in the operating room — and histopathologic examination of the specimens. All such cytologic and histologic specimens have been evaluated by one of us (L.B.W.). Tumors have been staged according to the recommendations of the American Joint Committee for Cancer Staging and End-Results Reporting.

RESULTS

From Nov 1, 1971, through July 30, 1976, 4,622 participants and 4,596 controls were entered in the study. Through March 1, 1978, tumors in the upper respiratory and alimentary pathways were detected in 18 participants and 19 controls, and lung cancer was found in 68 and 42, respectively (Table 1). All tumors in the upper respiratory and alimentary passages were squamous cell carcinomas, with one exception, an oncocytic adenocarcinoma of the larynx in one of the symptomatic control patients. The distribution of patients among the various disease stages in the two groups was similar (Table 2).

In the 18 participants, the search for cancer in the upper respiratory and alimentary passages was instigated by abnormal sputum cytologic findings in eight, onset of symptoms (for example, hoarseness, sore throat, sore in mouth) in nine, and findings on a routine head

TABLE 2. STAGE OF UPPER AIRWAY TUMORS IN MAYO LUNG PROJECT IN PARTICIPANTS AND CONTROLS

	Participants			*Controls*		
	Detection by:			*Detection by:*		
Stage	*Cytology*	*Symptoms*	*Total*	*Cytology*	*Symptoms*	*Total*
TIS	1	1	2	0	0	0
I	1	5	6	1	8	9
II	4	2	6	0	2*	2
III	1	0	1	0	3*	3
IV	1	1	2	0	2	2
NS†	0	0	0	1	3‡	4

*One patient had two primaries. †NS - Not staged. ‡One patient had adenocarcinoma of the larynx.

LIBRARY

TABLE 3. DETECTION OF UPPER AIRWAY CANCER IN MAYO LUNG PROJECT IN 18 PARTICIPANTS

Detection by:	*No.*	*Age, Mean (Range), Yr*	*Pack Years, Mean (Range)*	*Site of Cancer*
Sputum cytology	8	61 (50-70)	49 (25-75)	Larynx 5, base of tongue 2, tonsillar pillar 1
Symptoms*	9	60 (47-69)	62 (33-120)	Larynx 5, base of tongue 1, hypopharynx 1, floor of mouth 2
Examination†	1	59	100	Larynx

*All had negative results on sputum cytologic examination, but two temporarily dropped out and did not send sputum for approximately four years before experiencing symptoms.

†Otorhinolaryngologic examination for ear problem; negative results on cytologic study.

and neck examination for an ear problem in one (Table 3). In the 19 controls, the search began because symptoms developed in 17, or abnormal sputum cytologic findings were present in 2 (Table 4).

In one patient in the participant group who was found to have a squamous cell cancer of the anterior tonsillar pillar, adenocarcinoma of the lung developed subsequently. The second tumor was detected nine months after the intraoral cancer had been excised transorally.

Of the eight participant patients whose tumor was detected cytologically, three had involvement of the posterior (laryngeal) surface of the epiglottis, two of the right vocal cord, one of the left anterior tonsillar pillar, and two of the base of the tongue. Three of the tumors were small and were not readily detected on gross examination. Microscopically, all three were predominantly in situ, with focal microinvasion extending 0.1 to 0.3 cm in depth. Two patients had small lesions, 2 cm to 2.2 cm in diameter, with in situ and invasive components; in the latter case the lesion extended to a maximum depth of 0.6 cm.

Three cases of more advanced disease were encountered. In one, positive sputum cytologic findings were obtained during an 18-month period before detection of a squamous cell carcinoma of the posterior surface of the epiglottis. Three unsuccessful attempts at localization were carried out during this period. Treatment consisted of supraglottic laryngectomy and neck dissection. The resected tumor measured 5 by 3.5 by 1.5 cm and involved the entire posterior surface of the epiglottis with extension into the preepiglottic space. A jugular lymph node on the right side contained metastatic cancer. A second patient with advanced disease refused localization procedures for ten months after the cytologic test had become positive. Eventually, a palpable cervical node was noted, and the patient sought otohinolaryngologic consultation in his own community. The primary tumor involved the base of the tongue and adjacent pharyngeal wall and was staged T4N3M0. The third patient with advanced disease had a tumor involving the tongue-tonsillar area on the left with metastases to the left side of the neck (T2N1M0). He received irradiation and surgical treatment elsewhere.

TABLE 4. DETECTION OF UPPER AIRWAY CANCER IN MAYO LUNG PROJECT IN 19 CONTROLS

Detection by:	*No.*	*Age, Mean (Range), Yr*	*Pack Years, Mean (Range)*	*Site of Cancer*
Sputum cytology	2	67, 68	91	Larynx 2
Symptoms	17	64 (50-73)	60 (38-100)	Larynx 11, tongue 3, hypopharynx 1,* floor of mouth 3*

*One patient had two primary tumors.

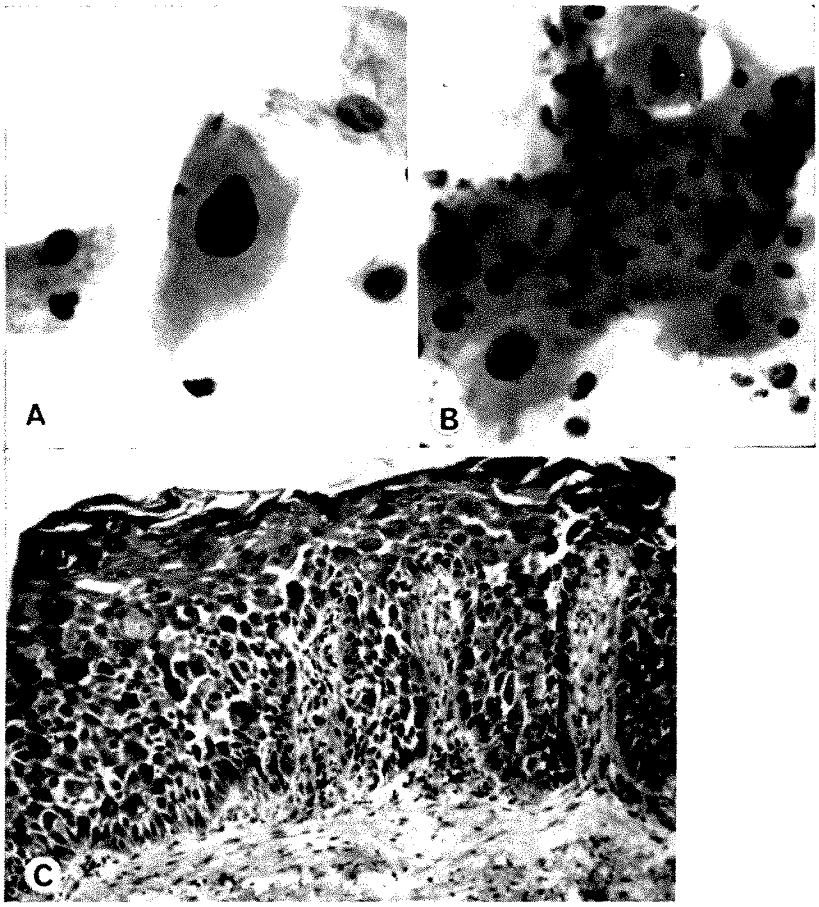

Fig. 1. Squamous cell carcinoma of vocal cord. A) Single markedly atypical squamous cell in sputum. B) Clump of atypical squamous cells showing pronounced keratinization. C) Histologic section of in situ squamous cell carcinoma with superficial keratin production. (X100)

Survival data are preliminary because follow-up still is of short duration in many instances. In the participant group it has been 2 to 48 months, and in the control group, 3 to 34 months. Among the participants (18), 12 are alive and free of tumor, 4 are alive with residual or recurrent tumor, 1 has acquired a lung cancer for which he is receiving chemotherapy, and 1 has died of a myocardial infarction but had been free of tumor two years after treatment. In the participant group, survival is similar in patients whose disease was detected by cytologic studies and in those in whom detection was based on the presence of symptoms.

Among controls (19), 14 are alive and free of tumor, 2 are alive with residual or recurrent tumor, 1 has died of the consequences of metastatic tumor, 1 has died of heart disease, and 1 has been lost to follow-up.

ILLUSTRATIVE CASES

Case 1. A 60-year-old male had sputum cytologic examinations during a two-year period. Sixteen months after the first examination, moderate squamous cell atypia was seen, and four months after that the cytologic findings were similar in five separate sputum specimens obtained over three months. The final specimen obtained at the end of the two-year period showed marked cellular atypia (suspicious for squamous cell carcinoma) (Fig. 1A and B). A complete otorhinolaryngologic examination was done, and a granular mass was seen on the midportion of the right vocal cord, which was mobile. Suspension laryngoscopy

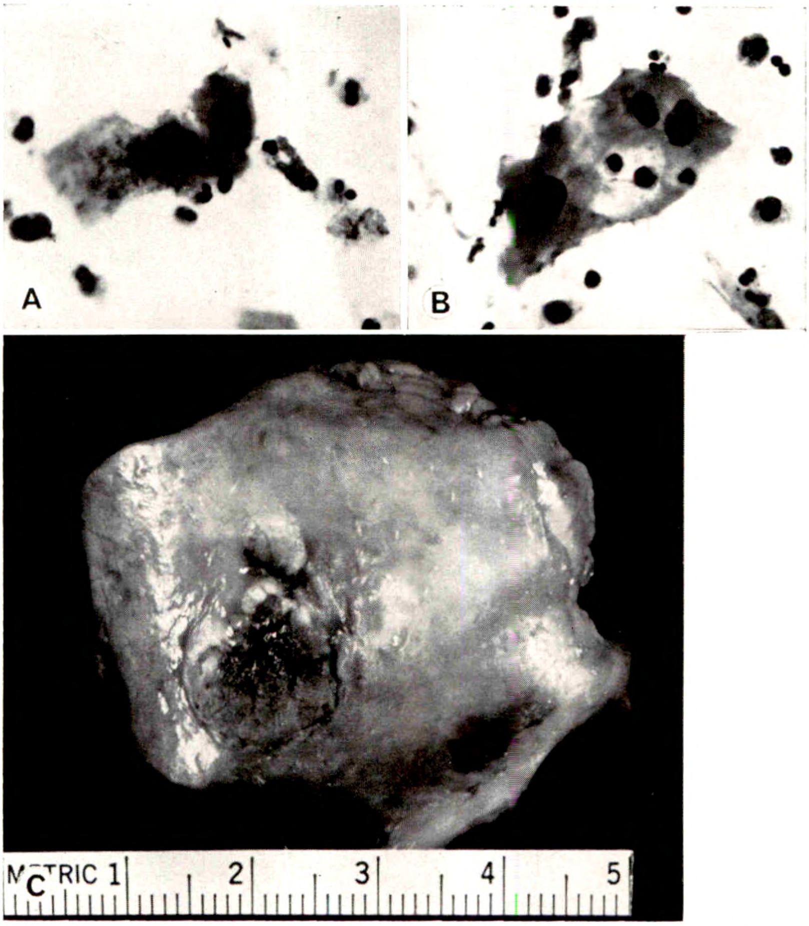

Fig. 2. Squamous cell carcinoma of epiglottis. A) B) Markedly atypical squamous cells in sputum. C) Resected epiglottis. In situ and superficially infiltrative squamous cell carcinoma on posterior surface.

was carried out, and a portion of the tumor was removed for frozen-section histopathologic assessment. Squamous cell carcinoma was identified in the specimen.

The involved vocal cord was excised transorally by means of electrocautery at the time of suspension laryngoscopy. Examination of the specimen showed Grade 1 squamous cell carcinoma, predominantly in situ but with focal superficial infiltration and marked surface keratinization (Fig. 1C). At present, four years postoperatively, there is no evidence of recurrence.

Case 2. A 55-year-old male had sputum cytologic examinations during a 5⅓-year period until cancer was found and surgery was undertaken. For the first two years, cytologic studies gave negative results, but slight cellular atypia was seen in subsequent specimens until 4⅓ years from the time of the initial specimen (1 year before surgery), when moderate squamous cell atypia was first noted. Several sputum specimens over the next nine months showed slight to moderate cellular atypia. Final specimens, three months and one month before surgery, showed moderate to marked atypia (suspicious for squamous cell carcinoma) (Fig. 2A, B). A complete otorhinolaryngologic examination was done, and an elevated region consistent with tumor, more extensive to the left of the midline, was seen on the posterior (laryngeal) surface of the epiglottis. No nodes were palpable in the neck. Histopathologic examination of a biopsy specimen removed at the time of suspension laryngoscopy showed infiltrative squamous cell carcinoma, and a left radical neck dissection and supraglottic laryngectomy were performed.

Examination of the surgical specimens from the epiglottis and the left radical neck dissection showed two areas of squamous cell carcinoma involving the posterior surface of the epiglottis near its midportion (Fig. 2C). The larger tumor was 1.1 cm in diameter and the smaller was 0.7 cm in diameter. Both were predominantly in situ, with foci of microinvasion to a maximum depth of 0.3 cm.

DISCUSSION

The Mayo Lung Project was undertaken primarily to evaluate a screening program for lung cancer in high-risk subjects. The discovery of several patients with tumors in the *upper* respiratory and alimentary passages by sputum cytologic examination illustrates the usefulness of screening and underscores the well-known fact that patients who are at risk for lung cancer are also at risk for squamous cell carcinoma in the head and neck region. This fact is buttressed by the observation that 37 of the 146 patients (25%) in the Mayo Lung Project who were found to have cancer through March 1, 1978, had tumors in the upper respiratory and alimentary passages. The search for these tumors in the head and neck was instigated by abnormal findings on sputum cytologic examination in ten patients — eight participants and two controls.

The case histories that were cited demonstrate that cytologic changes often pass through stages, from negative findings or slight atypia to moderate or marked atypia. This transition occurs during the course of months or several years, and the transition time appears to be quite variable. Symptoms may develop near the time that sputum cytologic tests become positive. All nine participants in whom symptoms developed and the one asymptomatic patient who had an otorhinolaryngologic examination for an unrelated problem had negative results on sputum cytologic studies on one or more occasions before the otorhinolaryngologic examination at which their tumors were detected. Thus, cytologic study may give negative results at the same time that cancer is readily detectable by a thorough office examination of the upper respiratory and alimentary passages. Further, the stage of the tumors appeared to be comparable in participants in whom tumors were detected cytologically and in those in whom they were detected on the basis of symptoms. Similarly, when all participants (those who were screened sequentially) and controls were compared, the various stages of the disease were equally represented in the two groups.

The survival data should be considered preliminary because follow-up has been less than five years in all instances. It does not appear that survival in the participant patients, including those whose examination was instigated by abnormal results of sputum cytologic study, is any better than that in the control patients, probably because the distribution of patients among the various disease stages in the two groups was similar. In contrast, it appears that survival after treatment is better in patients with cytologically detected (occult) lung cancer than it is in those in whom the lesion was at a more advanced and overt stage.[1,6]

Apparently, symptoms develop in close approximation to the time that results of sputum cytologic findings become abnormal in many of the patients with tumors in the upper airway. Questioning of high-risk patients about symptoms and a thorough examination of the upper respiratory and alimentary passages is the usual approach for early diagnosis; however, sputum cytologic examination in high-risk patients will reveal a significant number of these tumors.

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MUCOCILIARY TRANSPORT

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Our laboratory has developed bronchofiberscopic and roentgenographic techniques to measure tracheal, bronchial and nasal mucus velocities in humans and animals. We found that inhalation of specific antigen is associated with depression of tracheal mucus velocity in dogs who may or may not display bronchospasm and the mediator for this phenomenon might be SRS-A. Corroboration of the depression of tracheal mucus transport after ragweed inhalation has been obtained in susceptible asthmatic patients; prior inhalation of cromolyn blocks this reaction. Depression of tracheal mucus transport may be the earliest adverse manifestation of cigarette smoking in young subjects. Slowing of mucus transport in the bronchi occurs after suctioning with suction catheters; a newly designed suction catheter tip, the Aero-Flo®, displays less adverse effects on mucus velocity than standard end hole and side hole catheters. Nasal mucus velocity is enhanced by nasal decongestants, ingestion of hot fluids and exercise.

During the 1970 meeting of the American Broncho-Esophagological Association I was present when a film was being shown by Dr. Shigeto Ikeda[1] which was taken through a new instrument, the fiberoptic bronchoscope. A few days later, after a demonstration of the bronchofiberscope at Mt. Sinai Hospital, I developed a plan to answer questions which had plagued me several years: 1) the assessment of tracheobronchial damage in patients who were intubated, 2) a better way to carry out nasotracheal suction, and 3) collection of uncontaminated secretions from the lower airways for bacteriologic examination. In so doing, our group, who had never been involved with bronchoscopy, improvised new techniques for utilizing the instrument. We became the first group to employ a nasopharyngeal airway to facilitate transnasal introduction of the bronchofiberscope in nonintubated patients and we devised a T-adaptor to permit concurrent endoscopy while maintaining mechanical ventilation on intubated patients. These studies led to the design of a minimally traumatic suction catheter, the Aero-Flo® catheter. Shortly after this clinical progress, we received a grant from the National Heart and Lung Institute regarding oxygen toxicity.

I had known that the first symptoms of oxygen toxicity in normal volunteers might be related to tracheobronchitis and thought that earlier detection of damage might be accomplished by observing slowing of mucus transport in the trachea. With preliminary observations, we proposed a cinebronchofiberscopic method for estimation of tracheal mucus velocity during the breathing of high concentrations of inspired oxygen. The contract was awarded by the National Heart and Lung Institute and six months later the method for measuring tracheal mucus velocity was established.[2] It hinged upon calibrating the increase in image size on cine of Teflon® discs deposited on the mucosa to distance from the distal lens of the bronchofiberscope (Fig. 1). We computed velocity of individual discs as they moved to the distal lens by fixing the filming time and then calculated the average tracheal mucus velocity. We proved our hypothesis about oxygen toxicity: even after three hours of 100% oxygen breathing, normal subjects showed slowing of tracheal mucus transport without symptoms or changes in pulmonary function.[3]

I should like to review some of the more recent studies of mucociliary

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From the Mount Sinai Medical Center, Miami Beach, Florida. Supported in part by NHLBI Grant HL 17816.

Presented at the meeting of the American Broncho-Esophagological Association, Palm Beach, Florida, April 24-25, 1978.

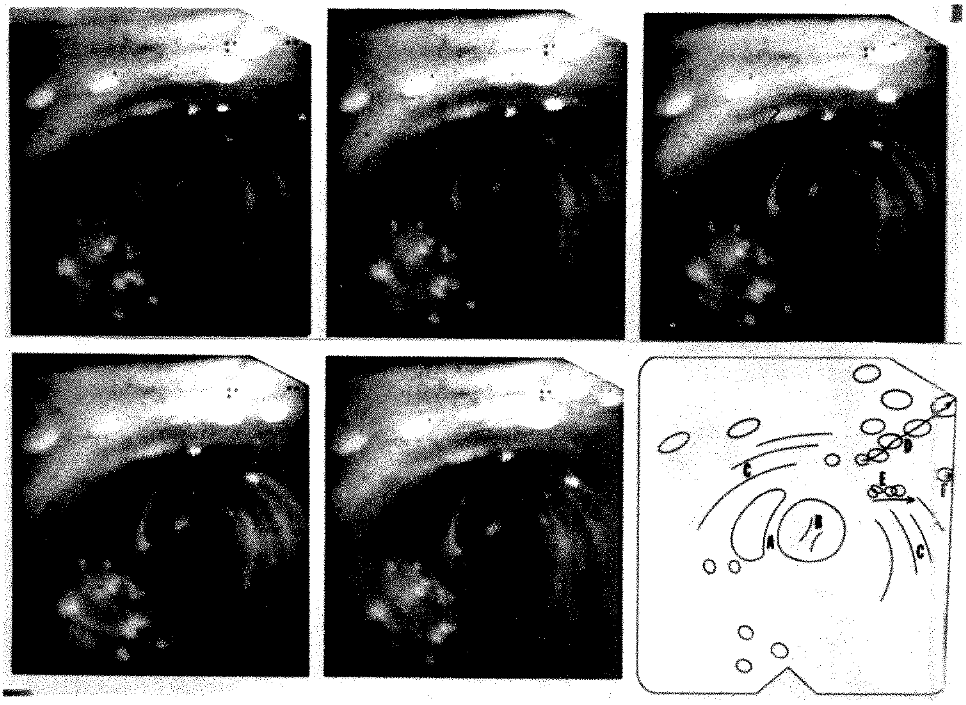

Fig. 1. Mucus velocity photograph sequence and particle path tracing in dogs. Photographs taken one minute apart. Tracing shows particle positions and tracheal features. A - Carina; B - Left bronchus; C - Tracheal ring; D, E, and F - Discs with motion.

clearance: 1) alterations of mucus transport in canine and human allergic asthma, 2) effects of chronic smoking on tracheal mucus velocity, 3) assessment of damage to the tracheobronchial mucosa produced by suctioning, and 4) modification of nasal mucus velocity by hot and cold water, chicken soup, decongestants and exercise.

In our early studies, tracheal mucus velocity was measured by the cinebronchofiberscopic method but lately we have employed a roentgenographic method which is less invasive and gives more reliable values.[4] Discs 1.0 by 0.8 mm composed of Teflon® mixed with 50% bismuth trioxide, to render them radiopaque, are insufflated into the trachea from the inner channel of the bronchofiberscope placed just above the vocal cords. With a fluoroscopic image intensifier, their motion along with a signal from a digital clock is recorded on videotape for subsequent data processing (Fig. 2). The distance moved relative to a calibrated length of radiopaque Teflon® tape placed on the skin over the trachea is measured with a ruler over a 30 to 60 second period and converted to velocity. Approximately 20 discs are measured to compute tracheal mucus velocity. In young, normal nonsmokers, the mean velocity is about 10 mm/min and is not influenced by change in body position, viz, upright to supine. All discs deposited on the tracheal mucosa move cranially but in elderly nonsmokers, about 10% of discs display zero motion. In patients with excessive secretions and slow mucus velocity, the discs may move caudally in the upright position if they lodge in excessive secretions but do not exhibit this behavior in the supine position. These discs are designated as having zero not minus velocities since their caudal motion is related to gravitational effect.

BRONCHIAL ASTHMA

Although the hallmark of bronchial asthma is bronchospasm, Rigler and

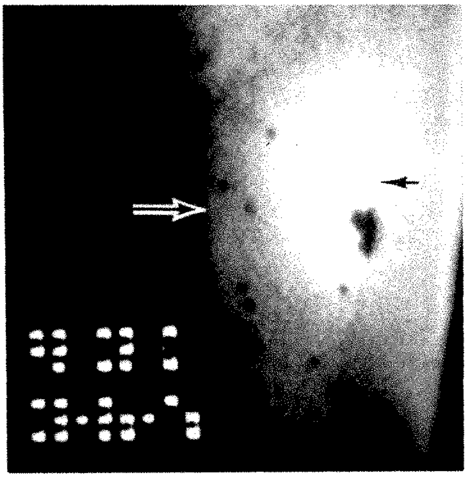

Fig. 2. Photographic copy (lateral view showing radiopaque discs in the proximal trachea). Arrows mark anterior (right) and posterior (left) walls of trachea. Time is displayed in left lower corner (Friedman et al: Am Rev Respir Dis 116:281-286, 1977).

Koucky,[5] by utilizing bronchographic techniques and postmortem examination, demonstrated that occlusion of smaller bronchi by mucus plugs both in mild and severe cases was an integral part of the asthmatic reaction. Dunnill[6] substantiated this finding from examination of necropsied lung specimens. To test this hypothesis physiologically, we initially utilized a canine model of experimental asthma.[7] Inhalation of *Ascaris suum* antigen by dogs who are skin test positive to this antigen produces acute bronchospasm with a duration of less than an hour in over half the animals initially challenged. Measurements of tracheal mucus velocity and specific respiratory conductance were obtained prior to aerosol challenge. Specific respiratory conductance is the reciprocal of respiratory resistance normalized to lung volume; a rise indicates bronchodilation, a fall bronchoconstriction. All dogs who were skin test positive to *A. suum* showed a decrease in tracheal mucus velocity to one third of baseline values within 45 minutes after breathing an aerosol of this antigen (Fig. 3). Only one half of them (reactors) responded with bronchospasm as measured by a significant reduction in specific respiratory conductance. Tracheal mucus velocity remained decreased at the end of the two-hour observation when specific respiratory conductance had returned to baseline values in the reactors. These studies demonstrated that impairment of mucociliary transport was not only an integral part of the asthmatic attack, but that it also could occur independently of bronchospasm. There was no change in tracheal mucus velocity and specific respiratory conductance after breathing aerosolized vehicle for the antigen as a control. Inhalation of *A. suum* antigen or ragweed antigen in skin test negative dogs did not alter tracheal mucus velocity nor specific

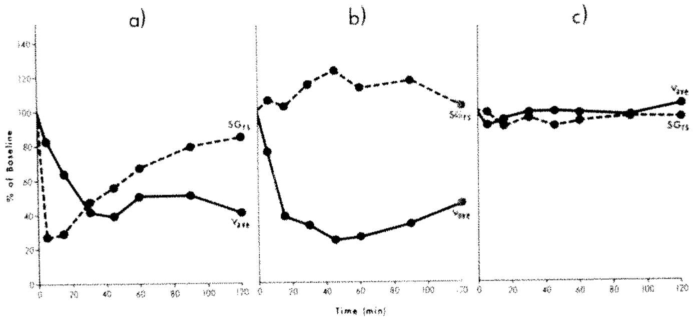

Fig. 3. Relative changes in total respiratory conductance (SC_{rs}) and average tracheal mucus velocity (V_{ave}) after antigen challenge in dogs sensitized to *A. suum* but not to ragweed extracts. Time 0 represents baseline values. Dogs who responded to *A. suum* antigen with bronchospasm (a); dogs with no bronchospastic response to *A. suum* challenge (b); control dog who breathed ragweed extract (c). (Wanner et al, J Appl Physiol 39:950-957, 1975.)

respiratory conductance indicating that the change in tracheal mucus velocity in sensitized animals was related to antigen-antibody reaction. Aerosols of acetylcholine and histamine increased tracheal mucus velocity, thereby excluding these mediators as the ones responsible for the impairment of mucus transport in the canine asthma. Nebulization of *A. suum* antigen, together with an experimental selective antagonist of slow reacting substance of anaphylaxis (SRS-A), produced a marked increase of tracheal mucus velocity regardless of whether or not bronchospasm was elicited. This suggested that SRS-A might be responsible for the decrease in tracheal mucus velocity possibly by altering mucus rheology since it is known to increase capillary permeability. Even though SRS-A appears to be released as a mediator during antigen-antibody reaction in the lung, it does not cause contraction of the smooth muscle of large bronchi. The explanation of the increase in tracheal mucus velocity after pretreatment with the SRS-A antagonist and antigen is uncertain but could be related to unmasking of the effects of mediators which increase mucus velocity, such as histamine and acetylcholine or formation of a new agent.

In adults with bronchial asthma during an asymptomatic phase, tracheal mucus velocity is slowed. McFadden[8] described several asthmatic patients who presented with exertional dyspnea, but who did not wheeze. Pulmonary function tests revealed peripheral airway dysfunction as evidenced by markedly elevated residual volume, frequency dependence of lung compliance and depressed flow rates in the middle-vital-capacity range, whereas specific airway conductance and FEV_1 were normal. The failure of frequency dependence of lung compliance and elevated residual volume to improve after bronchodilator treatment for several days indicated that there might be obstruction of the small airways by mucosal edema or mucus secretions. Similarly, in children with bronchial asthma, a three-month period of oral treatment with the beta adrenergic agonist, metaproterenol, failed to improve small airway obstruction.[9] Bronchoprovocation investigations have now been carried out by Mezey et al* in asthmatic patients who are skin-test positive to ragweed antigen. First, bronchoprovocation with antigen was used to establish a dose that would cause specific airway conductance to drop approximately 25% of the baseline in these asymptomatic subjects who had normal or near normal dynamic mechanics of breathing. On a subsequent day, after obtaining baseline values of specific airway conductance and tracheal mucus velocity, the same dose of antigen was administered to these volunteers. Fifteen minutes later, when specific airway conductance had fallen to 25% from baseline, tracheal mucus velocity showed the same decline. One hour later, specific airway conductance returned to normal but tracheal mucus velocity showed a further fall to 50% of the baseline. Appropriate placebo controls failed to alter specific airway conductance and tracheal mucus velocity. On another day, the volunteers then inhaled cromolyn, an agent which blocks the release of mediators from the mast cells present in the lungs. This agent did not affect specific airway conductance but caused tracheal mucus velocity to rise 30% above baseline. The rise in tracheal mucus velocity brought this value into the range of age-matched normal nonasthmatics. The asthmatics were then rechallenged with nebulized ragweed antigen. The sequence produced partial protection from bronchoconstriction and tracheal mucus velocity, instead of falling, rose an additional 35% over the value obtained prior to inhaling antigen. After an hour, tracheal mucus velocity returned toward the baseline value. Thus, prior cromolyn administration protected completely against the fall in tracheal mucus velocity after antigen challenge; the rise in tracheal mucus velocity was similar to that seen when the dogs were treated with the SRS-A blocker and further substantiates the role of mediator release as the basis for impaired mucus transport in asthma.

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*Mezey RJ, Cohn MA, Fernandez R, et al: Mucociliary transport in allergic patients with antigen induced bronchospasm, has been submitted for publication.

CHRONIC OBSTRUCTIVE LUNG DISEASE

There is marked slowing of tracheal mucus transport in patients with pulmonary emphysema and chronic bronchitis.[10,11] The values in such patients are less than 3 mm/min compared to normals who have values of 10 to 20 mm/min determined by the cinebronchofiberscopy method. Patients with chronic bronchitis who have measurements of tracheal mucus velocity by the radiopaque disc method demonstrate that over 85% of 25 to 30 discs in an individual subject do not move cranially during a ten-minute observation period. This occurred both in patients with the simple (chronic productive morning cough) and the obstructive (chronic productive morning cough plus airway obstruction) types of chronic bronchitis. In such patients, discs often move to and fro transversely but not upwards.

In some patients with chronic bronchitis who had as many as 60 discs deposited on the trachea, there was no cranial movement of any of the discs. Indeed, discs entrapped in mucus frequently slid caudally down the trachea due to gravity. In such patients, cough became the major mechanism for removal of tracheobronchial secretions (and discs). Voluntary coughing in patients with the obstructive type of chronic bronchitis was not nearly as effective in clearing discs as in the normal subjects who could remove all the discs in the trachea with a single explosive cough. This slowing of mucus transport has also been observed in patients with chronic bronchitis following inhalation of radioactive aerosol and external monitoring of radioactivity over the lungs. In the study by Camner et al,[12] 40% of such patients investigated had constant radioactivity over the chest for a two-hour period, implying zero mucus transport in the lungs.

In patients with chronic obstructive lung disease, subcutaneous administration of 0.25 mg terbutaline increased tracheal mucus velocity 15 minutes after injection two to three fold over baseline but even with this increase, values remained far below the normal range.[10] Unpublished observations of measurements of tracheal mucus velocity after inhalation of aerosolized fenoterol, another adrenergic agonist, indicated a less consistent improvement of mucus transport. This could be related to uneven deposition of the drug during inhalation such that the area measured, i.e., the trachea, received insufficient drug to produce a rise in tracheal mucus velocity or possibly that requirement for the drug to act on the wall of the trachea via the bloodstream. The latter notion is supported by the work of Nadel,[13] who found that terbutaline enhanced the pumping of chloride and water from the outer wall of the trachea to the lumen when placed in contact with the outer wall but not vice versa. Under such circumstances, the transfer of water to the lumen might improve the rheologic properties of mucus and facilitate transport of mucus.

Tracheal mucus velocity is generally decreased in adults with cystic fibrosis but occasional patients have values within the normal range.[14] Subcutaneous administration of terbutaline produces a similar rise in tracheal mucus velocity as in the patients with chronic obstructive lung disease.

SMOKING

In 1973, Wanner and associates[15] found that beagles who smoked one pack of cigarettes a day, five days a week for 13.5 patient months had depression of tracheal mucus velocity compared to a control group. In these animals, there were no adverse alterations of pulmonary resistance, dynamic lung compliance, single breath diffusing capacity, and arterial blood gases. These authors postulated that suppression of mucociliary activity associated with cigarette smoking might precede abnormalities of pulmonary function as determined by conventional methods. Recently, we confirmed these findings in man.[11] A group of young smokers age-matched to nonsmokers were identified who had normal lung volumes, and airway resistance. In about half the smokers, one or more tests of small airway obstruction, viz, closing volume, iso-flow-volume loop on air and helium-oxygen mixture, and multiple breath nitrogen washout at two different respiratory frequencies, were abnormal. The smokers could then be classified into two groups: those with normal pulmonary function and those with small airway disease. Both these groups had significantly lower tracheal mucus velocities than the normal nonsmokers. Many had zero mucus transport in the trachea but a history of cough could not always be elicited. However, Louden and Brown[16] have demonstrated that cough frequency and perception of cough by the patient often is markedly underestimated. About 50% of the deposited discs deposited on the tracheal mucosa had zero motion and the remainder were slower as a whole than in the nonsmokers. When the two groups of young smokers were separated, not on the basis of the presence of small airway disease, but on a mean tracheal mucus velocity value above or below 6.4 mm/min, the lowest value in the normal nonsmokers, then two patterns of distribution of disc velocities emerged. In the group with a normal average tracheal mucus velocity, the distribution of disc velocities was similar to the nonsmokers. In the group with mean tracheal mucus velocity less than 6.4 mm/min, the frequency histogram of disc velocities was similar to that observed in chronic bronchitis with 84% of the discs showing zero motion. Exsmokers who had stopped smoking 12-24 months showed the same two patterns of distribution of disc velocities.

Thus, depression of mucociliary transport and/or signs of small airway obstruction may present as the first manifestations of the deleterious effects of smoking on the lung. The depression of mucus transport in young smokers may be quantitatively similar to patients with chronic bronchitis of the simple or obstructive types. Exsmokers may continue to have slowed mucus transport long after discontinuance of smoking. Whether these young exsmokers go on in later life to develop clinically significant chronic bronchitis requires further investigation.

SUCTION CATHETER DAMAGE TO THE TRACHEOBRONCHIAL TREE

Up until 1956 most catheters designed to suction the tracheobronchial tree for removal of secretions did not provide for interrupted suction. In that year, Plum and Dunning[17] pointed out that suction catheters could draw in the mucosa of the airways in a manner similar to a crude biopsy. To minimize this hazard, they advocated interruption of vacuum to promptly relieve the drawing in of the mucosa. Over the years, this practice of interrupted suction has become a standard practice and certainly has contributed to the minimization of suction catheter damage. However, the basic design of suction catheters was not changed to minimize contact of the catheter with the mucosa, and even with interrupted suction, damage could still be produced.

Our group in 1972 reported that many patients who were intubated less than 24 hours showed extensive hemorrhages and erosions distal to the tip of the endotracheal tube in the region of the carina and within the right bronchus and its lower lobe branches, as observed by bronchofiberscopy.[18] We found that these lesions could be reproduced in anesthetized dogs by the then available standard end-hole, side-hole and end-hole and side-hole suction catheters as a result of invagination of the mucosa into the eyes of the catheter when vacuum was applied. More recently we also found that certain specially designed catheters to minimize this hazard also produced mucosal damage (Fig. 4). This observation of invagination of the airway mucosa into the eyes of the suction catheters led us to design a tip configuration which would prevent the eyes of the catheter from contacting the airway mucosa. A distal bead was placed at the end of an end-hole catheter as a mechanical impediment to prevent the end-hole from contacting the side walls of the airway

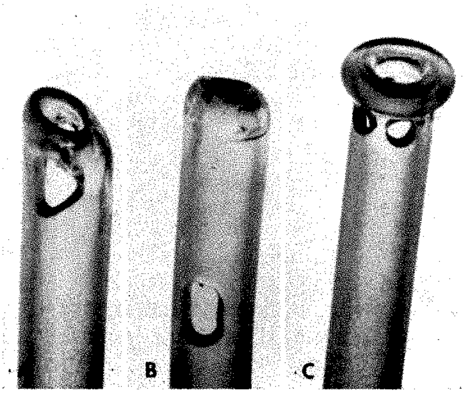

Fig. 4. Catheter tip configurations: A) Tri-Flo® tip, B) an end-hole and side-hole and C) the Aero-Flo® tip (Sackner: Tracheobronchial Toilet, Biomedia, 1978).

and four small holes were punched just proximal to the bead. The small holes served to vent the end hole if contact with the mucosa at a bifurcation occurred (Fig. 5). Together the bead and small sideholes promoted centering of the tip in the airway suctioned because of a favorable airflow pattern around the tip. The catheter tip has been designated as the Aero-Flo® Tip Suction Catheter. Histologic damage caused by this catheter was compared to a standard side-hole and end-hole catheter after suctioning every ten minutes for three hours. A few lesions were occasionally seen with the Aero-Flo® catheter microscopically, but both extensive gross and microscopic damage occurred with the standard suction catheter. We postulated that less damage with the Aero-Flo® catheter to the mucosa would preserve mucociliary clearance and tend to prevent colonization of the airways by pathogens.

We now have found that the Aero-Flo® catheter produces significantly less depression on mucociliary transport than the standard end-hole and side-hole suction catheter. Conscious sheep were tracheostomized under local anesthesia and a period of approximately one week was allowed to elapse to permit restoration of tracheal mucus velocity to the baseline value. Mucus velocity was measured in each bronchus by the radiopaque Teflon® disc method. Values for the right and left bronchial mucus velocity fell within 25% of the line of identity. Then one bronchus was suctioned continuously for 30 seconds utilizing two passes every ten minutes for three hours using either the standard or Aero-Flo® suction catheters. The suction catheter was guided into the main bronchus of choice by a Meditek® fiberoptic bronchoscope so that for a given experiment we could be sure that one bronchus was suctioned while the other served as a control. Bronchial mucus velocity was measured at the end of the suctioning procedure and 3, 21 and 27 hours later. The baseline value of the suctioned bronchus was compared to the nonsuctioned bronchus and a normalization factor was applied to account for slight changes with time in the nonsuctioned bronchus. The next week, suctioning was carried out on the contralateral main bronchus and the suction catheter

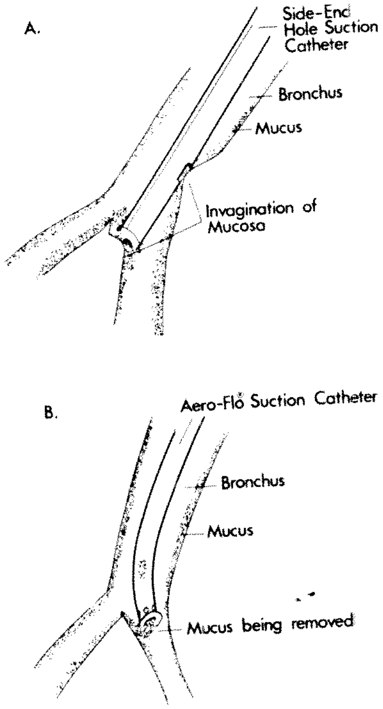

Fig. 5. Schematic of basis for suction catheter induced mucosal damage and alleviation by the Aero-Flo® tip design (Sackner: Tracheobronchial Toilet, Biomedia, 1978).

not employed in the first test. A significant difference was found between the Aero-Flo® and standard suction catheter, with the Aero-Flo® producing a much less depressive effect on bronchial mucus velocity at the end, 3 hours and 21 hours later. By 21 hours, the value of bronchial mucus velocity with the Aero-Flo® catheter had returned to the baseline value while the value was still below baseline with the standard catheter. Twenty-seven hours later, values after suctioning with either catheter had returned to the baseline. Similar results have been obtained in comparisons between the Aero-Flo® and the Tri-Flo® catheters.

NASAL MUCUS VELOCITY

During the past year, we modified the radiopaque Teflon® disc method to measure nasal mucus velocity. Discs were blown onto the superior surface of the mucosa overlying the inferior turbinate without topical anesthesia. The motion of these discs posteriorly from the level of the hard palate to 0.5 cm above it is measured with fluoroscopic image intensifier connected to videotape. The average velocity of five to ten discs is about 7.5 mm/min both in young and elderly nonsmokers. There is no significant variation over a 12-hour period and the coefficient of variation for repeated measurements daily over five days is about 30%. There was a poor correlation between the saccharin time (a particle of saccharin is placed on the nasal mucosa and the end-point is a sweet taste as it reaches the tongue by nasal transport) and our measurement of nasal mucus velocity. The saccharin time cannot be repeated for over an hour due to false end-points of the test, whereas our new method permitted repeated measurements within minutes.

EFFECTS OF INGESTED FLUIDS ON NASAL MUCUS VELOCITY

The annals of medical history are replete with folk remedies long used before the scientific demonstration of effectiveness. Thus, ingestion of various plants containing ascorbic acid and, cinchona bark, foxglove and rauwolfia root, with active ingredients of quinine, digitalis and reserpine, respectively, were employed hundreds of years prior to their introduction into clinical medicine.[20] Hot tea has been suggested as useful in the management of upper respiratory tract infections. Bang and associates[21] reported a significant increase in nasal mucus velocity of normal volunteers immediately after drinking approximately 500 ml of hot tea. Although not proved, an increase in nasal mucus velocity should be beneficial since it minimizes contact time of a pathogen deposited in the nasal mucus layer and thus prevents penetration into the mucosal layer. We wondered whether another folk remedy advocated for upper respiratory tract infections, hot chicken soup, might also display a similar action. Further, we wanted to investigate whether hot or cold liquids should be recommended as the fluid management in patients with upper respiratory tract infections, vis à vis effect on nasal mucus velocity.

We measured nasal mucus velocity and nasal airflow resistance in 15 healthy subjects before and at 5 and 30 minutes after drinking hot water by sip or straw, hot chicken soup by sip or straw and cold water by sip.[22] Hot water by sip increased nasal mucus velocity from 6.2 to 8.4 mm/min, hot chicken soup by sip from 6.9 to 9.2 mm/min and chicken soup by straw from 6.4 to 7.8 mm/min five minutes after administration. These increases were statistically significant compared to cold water, hot water by straw and a sham procedure. All values returned to their baselines at 30 minutes except cold water, which significantly decreased the nasal mucus velocity from 7.3 to 4.5 mm/min. No significant alterations in nasal airflow resistance occurred after the various treatments. We concluded that drinking hot fluids transiently increased nasal mucus velocity in part or totally through the nasal inhalation of water vapor. Hot chicken soup either through the aroma sensed at the posterior nares or through a mechanism related to taste appears to possess an additional substance for increasing nasal mucus velocity. Finally, hot liquids might be superior to cold liquids in the fluid management of upper respiratory infection.

EFFECTS OF NASAL DECONGESTANTS ON NASAL MUCUS VELOCITY

Topical nasal decongestants are often employed in the management of coryza and allergic rhinitis. They decrease nasal airflow resistance probably as a result of vasoconstriction which reduces the fluid content of the mucosa. We measured nasal mucus velocity in 13 healthy nonsmokers before and ten minutes after topical application of phenylephrine and tetrahydrozoline, alpha adrenergic nasal decongestant sprays.[19] Phenylephrine increased nasal mucus velocity from 8.4 to 13.7 mm/min and tetrahydrozoline from 8.1 to 13.8 mm/min, changes which were highly significant compared to vehicle, saline and sham placebos. We also measured nasal mucus velocity after phenylephrine spray in two patients with acute infectious rhinitis and noted a rise from 2.6 to 17.5 mm in one and from 4.5 to 7.1 mm/min in another. In a third patient with chronic rhinitis and sinusitis, nasal mucus velocity was 2.8 mm/min and remained at that value after phenylephrine spray. Thus, nasal decongestants might be beneficial in acute rhinitis to promote shortening of contact time on the mucosa of either antigen or pathogen. Our current efforts are being directed toward assessment of nasal mucus velocity and nasal airway resistance after provocation with ragweed pollen and the modification of this response by drugs.

EFFECT OF EXERCISE ON NASAL MUCUS VELOCITY

Unpublished studies from our laboratory showed that exercise for 20 minutes to a pulse rate of 130/min increased nasal mucus velocity in nine normal subjects from 7.6 to 12.7 mm/min. Five minutes following cessation of exercise, nasal mucus velocity returned to baseline value. Expiratory nasal resistance fell from 1.6 cm H_2O/liter x second to 0.6 cm H_2O/liter x second during exercise; and five minutes following cessation returned to baseline. Alpha adrenergic discharge appears to mediate these two potentially beneficial effects on nasal function. The decreased nasal airflow resistance promotes nasal breathing in such a way that noxious soluble gases in the asmosphere can be absorbed in the nose and particulates deposited on the nasal mucosa can be cleared more rapidly by nasal mucus transport.

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SECOND INTERNATIONAL SYMPOSIUM ON OTITIS MEDIA WITH EFFUSION

CALL FOR PAPERS

The Second International Symposium on Otitis Media with Effusion will be held May 9-11, 1979* at Ohio State University, Columbus, Ohio. Papers on the following topics will be considered by the program committee:

I. Definition and Classification

II. Epidemiology and Natural History

III. Etiology and Pathogenesis (Tubal Physiology and Pathology; Surface-Active Agent; Anatomy, Morphology, Pathology; Biochemistry, Pharmacology; Microbiology and Immunology).

IV. Identification, Diagnosis and Screening (Tubal Dysfunction; Microbiology for Bacterial Infection, Sensitivity Tests, Allergy; Biopsy and Cytology).

V. Management (Medical [Antibiotics, antihistamines, steroids, etc.]; Surgical [T&A, A, Tuboplasty, Ventilating Tube]; Educational management).

VI. Prevention (Vaccine, etc.)

VII. Outcome (Sequelae).

Please send a one-page abstract by September 1, 1978 to: David J. Lim, MD, Department of Otolaryngology, Ohio State University Hospitals, 456 Clinic Drive, Columbus, OH 43210.

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*Please note change in originally published date. Meeting has been scheduled definitely for May 9-11, 1979.

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EFFECTS OF VARIOUS DRUGS ON CANINE TRACHEAL MUCOCILIARY TRANSPORT

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A study of the effects of dehydration, atropine, terbutaline and N-acetylcysteine on canine tracheobronchial mucus is presented. Mucociliary clearance rates, mucus secretion volumes and mucus rheologic properties were studied. Clearance rates were studied by a radioisotope technique, mucus collected by a canine "tracheal pouch" method and rheologic studies performed on a microrheometer. Clearance rate was unaffected by dehydration and terbutaline, increased by N-acetylcysteine and decreased by atropine. Secretion volume was increased by terbutaline while dehydration and atropine were without effect. Rheologic factors were increased by dehydration and atropine while terbutaline was without an effect. The effects of N-acetylcysteine on secretion volume and rheologic properties could not be studied because of the nature of the techniques employed.

Mucociliary clearance has been studied for almost 150 years.[1] However, it was not until 1955 that the role of the mucus in this system was appreciated. In that year, Dalhamn confirmed what had first been reported almost 50 years earlier: i.e., mucostasis in the presence of normal beating cilia.[1,2] Dalhamn concluded that the composition and "quality" of the mucus secretion played an important role in determining the efficiency of the mucociliary clearance apparatus. Other investigators have claimed that the rheologic properties, production rate, volume, thickness and distribution and makeup of the various physicially different strata within the mucus layer play a role in determining clearance success.[3]

More recently rheology (viscoelastic behavior) has been implicated as a major determinant of clearance rate. This investigator in an in vivo canine study and other investigators in in vitro bullfrog studies have reported that mucociliary transport rates decrease as the elastic modulus (G′) increases.[4-6] Other investigators have attempted to alter mucociliary clearance as well as the mucus secretions by a variety of techniques which have either altered the normal physiologic state or introduced pharmacologic agents into the test system. Four such examples are systemic hydration, atropine, terbutaline and N-acetylcysteine.

METHODS AND MATERIALS

Mucociliary clearance studies, mucus collections and rheologic studies were performed on a weekly basis in five adult (6-10 kg) purebred female beagles in both the control and experimental states. Comparisons between each of the studied parameters (clearance rate, secretion volume, rheology) were made between control and experimental conditions.

In vivo mucociliary clearance was measured in the supine pentothal-anesthetized dog by a previously described radioactive γ emitting Na-pertechnetate solution technique.[7] Three to 5 μl of the pertechnetate solution were injected percutaneously into the tracheal lumen and the movement of this solution from one 3 mm tracheal cross-section to another similar section 35 mm more cephalad was the marker for mucociliary transport. This movement was

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Presented at the meeting of the American Broncho-Esophagological Association, Palm Beach, Florida, April 24-25, 1978.

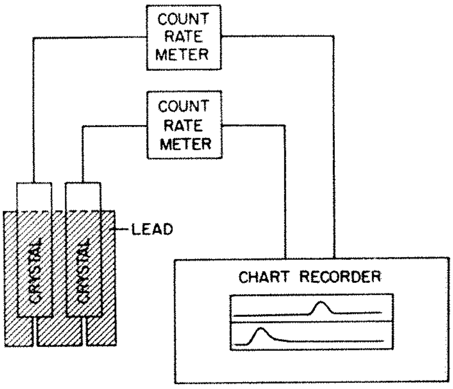

Fig. 1. Schematic of transport detection system.

followed by two NaI crystal scintillation detectors* connected to count rate meters** and chart recorders† which provided the records from which mucus transport times were determined (Fig. 1). By dividing the distance between the collimated detectors (35 mm) by the transport times, clearance velocities were obtained. Rectal temperatures ranged between 37-39 C and only one clearance measurement per dog was made on a test day.

Mucus collection was achieved by means of a canine tracheal pouch prepared by the methods of Wardell et al.[8] Measured volumes between 0.5-4.0 ml were collected by large bore needle aspiration of the pouch lumen.

After collection, all samples were stored at 4 C and tested within 24 hours at 37 C using the microrheometric method of Lutz et al (Fig. 2). This is a dynamic frequency response method of studying rheologic behavior, which employs the recording of the oscillation amplitude of a 100-200 μm iron sphere driven by sinusoidal electromagnetic forces. Data obtained by this method are in the form of G′ (storage modulus) and G″ (loss modulus) vs frequency of oscillation. The former coefficient (G′) is indicative of elastic behavior, while the latter (G″) is a measure of viscous behavior. Figure 3 shows typical tracings obtained. Values of G′ and G″ at 20 Hz were recorded as 20 Hz is both a good estimate of the rate of mammalian ciliary beating,[10] as well

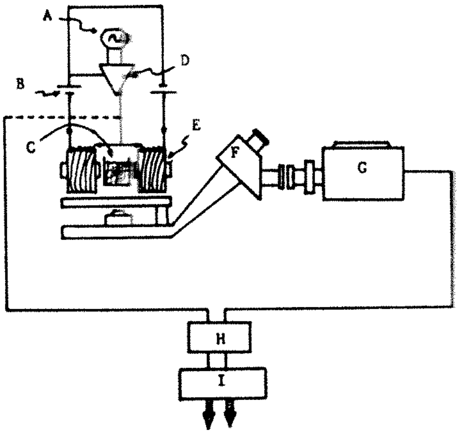

Fig. 2. Diagram of oscillating magnetic microrheometer. A - Sine wave generator; B - D.C. power supplies; C - Mucus and sphere; D - D.C. power amplifier; E - Electromagnets; F - Lietz inverted microscope; G - Optron tracker; H - Analog computer; I - Brush recorder.

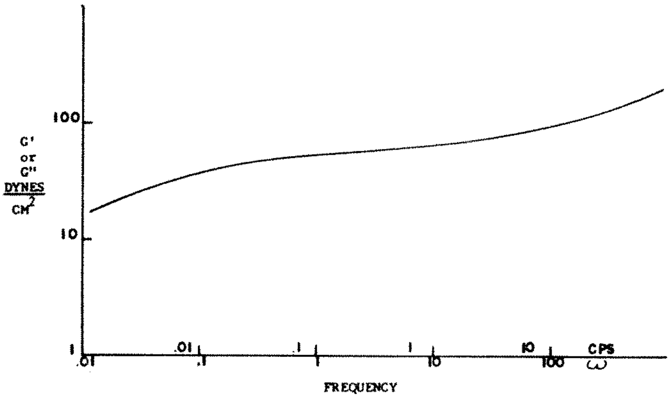

Fig. 3. G′ or G″ versus frequency. Frequency expressed as cps = cycles per second or ω = radians/sec = 2π· cps.

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*No. 6S4/1.5 Integral Line Assembly. Harshaw Chemical Co., Solon, OH.
**Nuclear Chicago 1620. Searle Analytic, Inc., Des Plaines, IL.
†Sanborn Twin-Viso 60-1300. Sanborn Co., Cambridge, MA.

TABLE 1. DEHYDRATION STUDIES

	Control					*Dehydrated*		
Vel	*Vol*	*G′*	*G″*		*Vel*	*Vol*	*G′*	*G″*
Dog 1								
11.1	3.0	14	8		19.1	4.0	15	18
14.0	3.0	27	13		17.5			
12.4	3.0	15	12		17.5	4.0		
13.1		54	39		9.1	4.5	105	64
Dog 2								
10.5	2.5	90	46		14.0	2.0	130	60
11.7	2.6	43	40		10.5	1.8	340	200
13.1	2.4	90	50		10.0	2.2	70	64
14.0	2.2	65	36		10.0	1.2	145	150
Dog 3								
11.1	1.3	132	96		12.4	1.0	250	150
13.1	1.2	135	60		7.8	1.0		
9.5	1.0	208	230		12.4	2.0		
11.7	1.1	96	96		14.0	1.0		
Dog 4								
7.8	1.4	470	210		5.4			
8.4	2.0	365	165		9.5	2.7	840	540
11.1					13.1	0.3		
15.0					15.0	0.2	780	500
Dog 5								
6.8	2.1	295	157		6.2	1.6	440	150
9.1	1.2	325	180		5.0	2.0		
6.2	1.5	440	175		3.5			
11.1	1.3	225	230		11.1	1.7	220	230
				Totals				
11.0	1.9	171	102	Mean	11.2	1.9	303	193
2.4	0.7	149	80	±S.D.	4.3	1.2	279	174
				P	>.9	>.9	<.02	<.05

Vel - Velocity in mm/min.
Vol - Volume in ml.
G′ - Elastic modulus in dynes/cm^2 at $\omega = 126$.
G″ - Loss modulus in dynes/cm^2 at $\omega = 126$.
P - Probability (*t*-test for paired samples).

as the frequency which best correlates rheologic parameters with clearance rates.[4]

All dogs followed the same experimental sequence, with each testing period lasting two to three weeks. The sequence was as follows: control, dehydration, control, atropine, control, terbutaline, control, N-acetylcysteine, control.

Dehydration was reached by allowing each dog only 75 cc water per day, resulting in a 6% average loss of body weight. Dehydration data was not recorded until the dogs had been treated for 14 days to allow for equilibration. Atropinization was achieved by twice daily subcutaneous injections of 0.1 mg/kg atropine sulfate. Terbutaline was given as oral terbutaline sulfate, 5.0 mg twice a day. N-acetylcysteine was administered as a 20% aerosol over a 20-minute time period with the exposure commencing ten minutes prior to the beginning of the clearance measurement. The aerosol was delivered from a DeVilbiss nebulizer via an endotracheal tube positioned just cephalad to the vocal cords. No mucus samples were collected when N-acetylcysteine was used.

RESULTS

Tables 1-4 present the results for the dehydration, atropine, terbutaline and N-acetylcysteine studies, respectively.

Dehydration. Volume of secretion and clearance velocity were unaffected, while both G′ ($P < .02$) and G″ ($P < .05$) were significantly higher when compared to matched controls (*t*-test for paired observations) (Table 1).

TABLE 2. ATROPINE STUDIES

Control					Atropine			
Vel	*Vol*	*G′*	*G″*		*Vel*	*Vol*	*G′*	*G′*
Dog 1								
14.0	3.0	27	13		10.5	4.0	51	45
12.4	3.0	15	12		11.1	3.2	36	30
13.1		54	39		13.0	3.2	36	21
Dog 2								
14.0	2.2	65	36		13.1	1.8	70	140
17.5	1.6	150	130		10.5	1.6	90	62
9.5	2.0	78	60		9.6	2.6	70	54
Dog 3								
14.0	1.0	140	210		10.5	1.0	180	240
17.5	1.2	172	265		3.4	1.0	175	96
7.6	1.2	130	100		7.3	1.2	450	440
Dog 4								
8.4	1.4	190	175		9.5	1.2	98	260
8.4	1.8	170	170		13.1	0.8	160	170
Dog 5								
17.5	1.3	355	355		5.2	1.3	290	750
8.4	1.4	148	112		6.6		175	190
10.5	1.6	128	270		9.1	1.4	215	220
				Totals				
12.3	1.7	130	134	Mean	9.8	1.9	150	194
3.6	0.6	85	107	±S.D.	2.4	1.0	115	197
				P	<.05	>.9	<.5	<.2

Atropine. Volume of secretion and G′ were unaffected while clearance rate was decreased ($P < .05$). There was also a tendency to increase G″ at the $P < .2$ level (Table 2).

Terbutaline. There was a consistent but small increase in secretion volume ($P < .02$) while clearance rate, G′ and G″ were unaffected (Table 3).

N-acetylcysteine. Clearance rate was significantly increased ($P < .001$) (Table 4).

DISCUSSION

Dehydration. It is generally thought that dehydration has an adverse effect on mucociliary clearance.[10] Both Baetjer[11] and Bang and Bang[12] have shown this to be the case with acutely dehydrated herring gulls and chickens. In clinical practice it is thought that dehydration results in thickened secretions with increased viscosity, with the result that the ability of the mucociliary escalator to transport and the patient's ability to expectorate the secretions are decreased. Our results are contrary to these beliefs. Both Baetjer[11] and Bang and Bang[12] studied the effects of acute dehydration on clearance rates in cold blooded animals, while we studied chronic dehydration in warm blooded animals. This perhaps is an explanation for the difference in results.

Intuitively, it would be thought that dehydration should decrease the rate of mucus secretion. However, our findings as well as those of Boyd and Boyd[13] fail to suport this belief. The increases in both G′ and G″ with dehydration support the empiric belief that hydration has an effect on rheologic properties. Since the volume of secretion did not change, it must be assumed that the increased viscoelastic moduli were the result of increased concentration of the glycoprotein secretion, a change in the quality or components of the glycoproteins and/or experimental error.

Atropine. Asmundsson and Kilburne in a recent review have reported that

TABLE 3. TERBUTALINE STUDIES

	Control					*Terbutaline*		
Vel	*Vol*	*G'*	*G''*		*Vel*	*Vol*	*G'*	*G''*
Dog 1								
17.5	2.6	58	39		16.2	4.0	74	46
15.0	3.0	23	17		10.5	3.0	80	63
12.4	2.6	40	29		16.2	3.0	108	112
Dog 2								
9.5	2.0	78	60		23.4	2.6	80	70
13.1	2.1	132	105		19.1	3.0	148	120
14.0	2.0	138	130		13.1	2.6	78	54
Dog 3								
8.8	0.8	330	250		5.1	1.6	410	300
8.4	1.2	330	340		4.5	1.6	120	140
11.1	0.8	210	290		13.1	1.0	125	160
Dog 4								
11.7	1.6	205	240		15.0	1.6		
7.0	2.4	220	220		15.0	2.0	370	190
6.8	1.8	230	225		8.4	1.8	175	290
				Totals				
11.3	1.9	166	162	Mean	12.8	2.3	161	140
3.3	0.7	107	112	±S.D.	5.1	0.8	118	89
				P	$<.5$	$<.02$	$>.9$	$<.6$

atropine generally slows mucus transport rates in vertebrates.[10] Our review of the literature was rather surprising in that there were few studies concerning the effects of atropine on secretion volume [14-16] and none dealing with its effects on mucus rheology. Both Florey et al[14] studying cats, and Basch et al[15] in humans reported the subjective impression that atropine decreased the volume of secretions. Boyd and Munro[16] reported that atropine caused a 20% decrease in respiratory tract fluid output in cats and dogs. It has been demonstrated physiologically, pharmacologically[14] and histochemically[8] that the submucosal tracheal acinar glands are parasympathetically innervated, while the mucosal goblet cells are not.

Since the goblet cells contribute a large percentage of the normal tracheobronchial secretions and they are not parasympathetically innervated, atropine would not be expected to have much effect on either the quantitative or qualitative aspects of the mucus secretions. Our data on secretion volumes and rheologic parameters support the above hypothesis. Our findings that atropine decreases clearance rate ($P <$ .05) is in good agreement with those studies already in the literature.[10]

The mechanism of how atropine decreases clearance rate is not known; however, we believe that our study supports the hypothesis that atropine decreases clearance rate by an effect on ciliary dynamics. Another possible site would be the periciliary fluid, but since this fluid is thought to be a ciliated epithelial transudate,[17,18] little support can be generated for this idea. However, Blair and Woods[19] have reported that $0.25\mu g$ of topically applied atropine decreased the ciliary beating rate 25% simultaneous with a clearance rate decrease of 45%. This study in conjunction with our data supports the hypothesis that the cilia are a major site of atropine's effect on mucociliary clearance.

Terbutaline. Santa Cruz et al[20] and Wood et al,[21] using a bronchofiberscopic technique, have shown that subcutaneous terbutaline sulfate improves mucus clearance in patients with obstructive lung disease and cystic fibrosis respectively, while it is without effect

TABLE 4. N-ACETYLCYSTEINE

	Clearance Rates (mm/min)					
Dog No.		*Control*			*N-acetylcysteine*	
1	17.5	15.0	12.4	21.0	23.3	21.0
2	9.5	13.1	14.0	14.0	16.2	17.5
3	8.8	8.4	11.1	9.5	13.1	17.5
4	11.7	7.0	6.8	21.0	17.5	21.0
5	11.7	6.8	6.6	17.5	23.3	15.0
Mean ±S.D.		10.7 ± 3.4			17.9 ± 3.9	
					$P < .001$	

in normals. Santa Cruz et al have also referred to unpublished data in which subcutaneous terbutaline did not affect tracheal mucus velocity in anesthetized dogs.[20] Our findings are in good agreement with those of Santa Cruz et al.

In their study, Wood et al[21] also reported the impression that there was an increased mucus secretion volume following terbutaline and this might have a role in increased clearance. They attributed the increased volume to either an increased rate of secretion or to an increased mobilization of secretions already present in the airways. Our data supports the concept that terbutaline increases the rate of mucus secretion. Terbutaline in our study had no effect on the rheologic properties of the mucus secretions. Thus in conclusion, it appears that terbutaline has little qualitative effect on tracheobronchial secretions but does cause a significantly small increase in secretion volume.

N-acetylcysteine. Acetylcysteine, a sulfhydryl mucolytic agent, is one of the mainstays of respiratory inhalation therapy. Its mucolytic activity resides in the sulfhydryl group which causes the oxidation-reduction depolymerization of the long chain disulfide-bound glycoproteins.[22] This reaction results in a decrease in G′ and G″. Because of its irritant effects, acetylcysteine might also cause a reflex hypersecretion of mucus.

Both of these above mentioned actions might enable a patient to mobilize his tracheobronchial secretions more effectively. This increased mobilization might be interpreted as an increased mucus transport rate as reported in this study. We have data to show that decreased G′[4] and increased secretion rates (unpublished) are associated with increased clearance rates. However, Medici and Chodosh[23] have recently shown that in humans inhalation of 10% acetylcysteine results in an initial decrease in viscosity simultaneously with no change or a decrease in secretion volume. Thus, their findings tend to refute the hypersecretion of mucus as a cause of increased mucus transport rate as hypothesized in this paper.

CONCLUSIONS

1. Dehydration to the extent of 6% body weight reduction had no effect on clearance rate or secretion volume, but resulted in an increase in both storage (G′) and loss (G″) moduli of respiratory mucus. The increased G′ and G″ are probably related to an increased concentration of the glycoprotein secretion and/or a change in the quality or components of the glycoproteins.

2. Atropine decreased the tracheal mucus clearance rate and slightly increased G″. G′ and secretion volume were unaffected. Atropine's effect on clearance rate is thought to be mediated by an effect on ciliary dynamics.

3. Terbutaline caused a consistent, slight increase in secretion volume, but was without effect on clearance rate, G′ and G″.

4. N-acetylcysteine inhalation resulted in an increased mucociliary transport rate, the basis for which might be a reduction in elastic moduli or possibly a reflex hypersecretion of mucus.

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VASCULARIZED HYOID INTERPOSITION FOR SUBGLOTTIC AND UPPER TRACHEAL STENOSIS

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Chronic subglottic and upper tracheal stenosis can be treated successfully with lumenal augmentation using a vascularized hyoid-sternohyoid muscle interposition into the stenotic area. Successful decannulation was achieved in eight of nine patients. Follow-up periods varied from 6 months to 36 months. Concomitant laryngeal stenosis and vocal cord paralysis were treated successfully at the same time. The major complication was occasionally delayed but successful decannulation due to granulation tissue. Minimal wound and peritracheal stoma infections probably accounted for the granulation tissue.

Chronic subglottic and upper tracheal stenosis remains a dilemma, as attested to by numerous articles proposing a variety of treatment modalities. Mild to moderate stenosis can occasionally be treated with repeated dilatations. Severe stenosis usually requires lumen enhancement of the stenotic area.

The use of hyoid-sternohyoid muscle interposition is a successful treatment for severe, chronic subglottic and upper tracheal stenosis. Canine studies by the present authors have shown good results.[1] The successful clinical application of the technique has been reported by Ward et al[2] and this report summarizes our own experience.

REVIEW

Chronic subglottic and upper tracheal stenosis is encountered in many circumstances. Among these, prolonged intubation is a leading factor. Some other causes include: congenital stenosis, blunt or penetrating neck trauma, high tracheotomy, caustic injuries, sarcoidosis, Wegener's granulomatosis, and relapsing perichondritis.[3]

The treatments for this problem are many. These can be categorized into four basic types: 1) dilatation with/without injection of corticosteroids; 2) dilatation and prolonged stenting; 3) lumenal augmentation; and 4) resection of the stenosis and primary reanastomosis.

Fearon and Ellis,[4] Holinger et al[5] and Hawkins[6] have reported successful results in 70-80% of patients treated with dilatation. Waggoner et al[7] likewise reported success with dilatation and injection of corticosteroids in a limited number of patients.

Crysdale and Platt,[8] and Goode and Shinn[9] have reported satisfactory results with prolonged stenting of the stenotic area. Crysdale divided the anterior and posterior cricoid in addition to the stenting.

The principle of lumenal augmentation has been described by multiple investigators. Augmentation of the stenotic lumen has been reported by using auricular cartilage,[10] composite clavicular bone muscular skin flap,[11] nasal septal graft,[12,13] costal cartilage autograft,[14] thyroid cartilage interposition,[15] and hyoid bone interposition.[1,16] Lu-

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menal enhancement with prosthetic material has also been described.[17,18]

Tracheal resection[19,20] is useful for upper tracheal stenosis which does not involve the immediate subglottic area. The resection of subglottic stenosis and thyrotracheal anastomosis[17,21] is a method of repair for immediate subglottic stenosis. Reconstruction of a long segment of subglottic and upper tracheal stenosis is not feasible by this technique. Furthermore, the likelihood of recurrent laryngeal nerve injury is enhanced.

The use of hyoid interposition for lumenal augmentation of laryngeal, subglottic and upper tracheal stenosis has been recognized to be a satisfactory method. Looper[22] in 1938 used a composite hyoid bone-muscle graft in the repair of laryngeal stenosis in a single case. Bennett[23] in 1960 used a similar hyoid repair with partial success.

Delahunty et al[24] first used free cricoid arch interposition in dogs in 1970. Alonso et al[16] utilized this technique successfully in five of six patients.

The vascularized hyoid-sternohyoid muscle interposition was felt to be a logical progression and improvement of the technique. The free hyoid graft can result in resorption. The present authors first used the vascularized hyoid bone in dogs with excellent results in dogs with previously created severe cricoid stenosis.[1] Ward et al[2] used this method successfully in three out of four patients.

METHODS AND MATERIALS

Evaluation. Thorough evaluation of the upper and lower airway is mandatory prior to surgery. The larynx must be examined for laryngeal stenosis, web, and vocal cord paralysis. Endoscopic evaluation is important since the actual lumen can differ significantly from air tomogram or contrast laryngotracheographic evaluation. A 50% decrease in lumenal diameter results in a 75% decrease in lumenal area.

Laryngotracheogram is important in defining the length of the stenotic segment. Air tomograms of the larynx and trachea or contrast laryngotracheogram can be used. We prefer the latter.

Most patients have moderate to long term tracheotomies, hence evaluation must be made to rule out distal tracheal stenosis or malacia. Coexisting stenotic or malacic segment in the distal trachea is not corrected by the operation and will prevent decannulation.

Pulmonary function tests are necessary, as patients with severe lower airway problems may be poor candidates. A temporary delay in tracheobronchial secretion clearance frequently occurs until complete respiratory reepithelization.

Procedure. The operation is performed under general anesthesia and a preliminary tracheotomy is performed (if not already present). The neck is hyperextended. A transverse incision at the level of the cricoid is made. Dissection is carried beneath the platysma and the skin flaps are elevated at least 2 cm above the hyoid superiorly, into the upper tracheal segment inferiorly; and laterally to the anterior border of the sternocleidomastoid muscles. In those patients with upper tracheal stenosis, the elevation is carried further inferiorly to the tracheal stoma. Adequate exposure of the strap muscles is mandatory. A vertical incision is made in the median raphe between the strap muscles with exposure of the larynx, cricoid, and trachea. The thyroid isthmus is transected for complete exposure.

An anterior midline incision is made through the cricoid and into the subglottic and upper tracheal stenotic area. If there is a concomitant laryngeal stenosis, web, or vocal cord paralysis, a laryngofissure is added. When an upper tracheal stenosis is present, the upper tracheal cartilages are incised anteriorly and midline to the level of the first nonstenotic tracheal cartilage. The tracheal stenosis may extend down to the tracheotomy site, and this will need to be revised through a lower ring before proceeding with the reconstruction. When there is a concomitant vocal cord paralysis, an arytenoidectomy and lateralization through the laryngofissure is carried out at this time.

After evaluating the length of stenotic area, the segment of hyoid to be removed is determined. Removal of the middle segment of the hyoid just lateral to each inferior cornu is usually sufficient. A longer segment of the hyoid can be removed for long segments of subglottic and tracheal stenosis. Injury to the superior laryngeal nerve is avoided. The suprahyoid musculature above the segment of the hyoid to be removed is incised. A 2-3 cm strip of inferiorly based sternohyoid muscle is left attached to the interposed hyoid segment on one side. The opposite sternohyoid muscle is transected at the hyoid. The segment of hyoid is then removed and interposed into the previous vertical incision through the stenotic cricoid and tracheal area in a vertical manner. Using perforating burrs, holes are drilled into the hyoid bone on all four corners. Care must be taken to undermine only the periosteum of that portion where the hole is to be drilled. The rest of the periosteum is left undisturbed and attached to the sternohyoid musculature. Corresponding holes are made in the cricoid and tracheal areas, and the hyoid is secured with

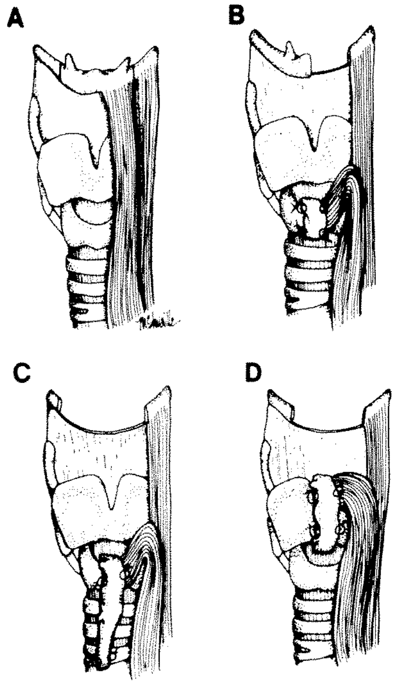

Fig. 1. Technique of vascularized hyoid interposition. A) Middle portion of hyoid used: 2-3 cm strip of one sternohyoid muscle is left attached to the hyoid. B) Interposed hyoid for subglottic stenosis. C) Interposed hyoid for subglottic and upper tracheal stenosis: longer segment of hyoid is used. D) Interposed hyoid for laryngeal stenosis.

No. 30 wire or microfilament sutures (Figs. 1 and 2).

With moderate stenosis, a laryngeal stent is not placed. With severe stenosis, the use of a Montgomery Silastic® laryngotracheal stent is recommended.

As this procedure only augments the anterior lumen and the stenosis is frequently circumferential, the lateral and posterior stenotic area can be treated by one of several methods. It can be injected directly with corticosteroids. The stenotic area can be excised and covered with buccal mucosal or split thickness skin graft over a stent. A superiorly based U-shaped mucosal flap may be elevated, taking care not to violate the posterior commissure area. The submucosal scar tissue is then excised down to the cricoid cartilage, and the U-shaped superiorly based mucosal flap is sutured back in place and a stent applied (Fig. 3).

After the placement of the hyoid, the strap muscles are reapproximated in the midline and the wound is closed in layers. A Penrose drain is always used. Antibiotics are used; preoperative antibiotics are recommended and are to be followed by a five to seven-day course postoperatively.

When a stent is used, it is left in for four to six weeks and removed endoscopically. The larynx, subglottis and trachea are evaluated endoscopically to verify an adequate airway before decannulation. In those patients without placement of a stent, repeat endoscopy is recommended in two weeks and if there is an adequate airway, decannulation is performed.

RESULTS

Nine patients had the vascularized hyoid interposition for chronic subglottic and/or upper tracheal stenosis. Five were seen at the Johns Hopkins Hospital and four the University of Colorado Medical Center.

Age, sex, and tracheotomy. The age of patients at the time of the surgical correction ranged from 7 years to 43 years, with the majority from 12-25 years. There were five male and four female. All patients had tracheotomies, ranging in duration from two months to 14 years.

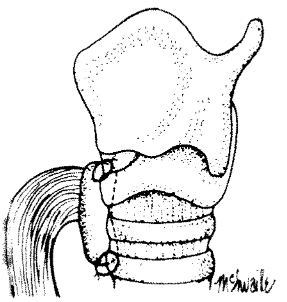

Fig. 2. Vascularized hyoid interposition: lateral view. Concavity of hyoid on lumenal surface enhances lumen.

Etiology. The etiologies of the stenosis varied. Three patients had stenosis secondary to prolonged intubation and/or high tracheotomy. Three patients had fractured larynx and/or cricoid and upper tracheal area sustained in motor vehicle accidents. One patient had congenital subglottic stenosis. One patient had subglottic stenosis secondary to relapsing perichondritis. Another had stenosis secondary to hot dust inhalation and multiple intubations for unrelated surgical procedures.

Previous Therapy. Other previous therapy to correct the stenosis had been

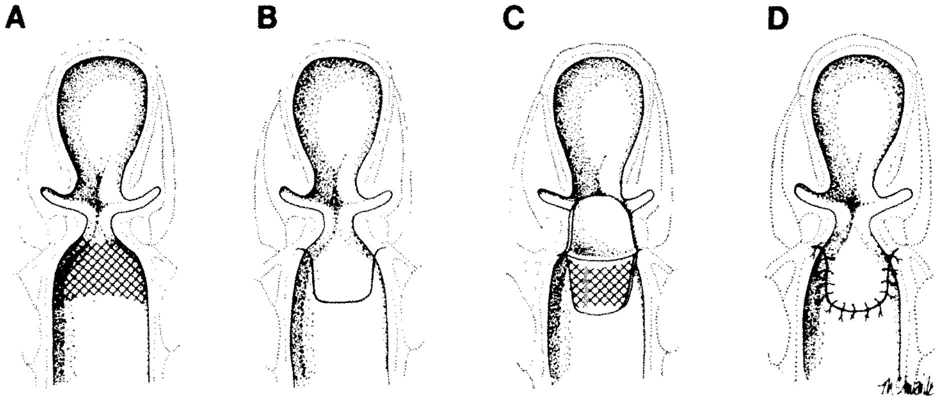

Fig. 3. Posterior subglottic stenosis repair. A) Area of posterior subglottic stenosis. B) U-shaped superiorly based mucosal flap is incised over posterolateral and posterior stenotic area. C) Mucosal flap elevated; submucosal scar tissue down to the cricoid cartilage is excised. D) Mucosal flap is reapproximated with suture. Stent must be placed.

tried in 7 patients. Repeated dilatations and corticosteroid injections had been used in seven. Excision of the stenotic site and prolonged stenting were also tried in two of the seven. Only two patients had no previous treatment and they had severe stenosis with 2-3 mm lumens.

Associated Laryngeal Problems. Concomitant laryngeal problems were found in five patients. Four had bilateral vocal cord paralysis with the vocal cords in paramedian position. Two had anterior glottic webs and one had laryngeal stenosis.

TABLE 1. SITES OF INVOLVEMENT

Site	*No. Patients*
Subglottis	3
Larynx/subglottis	3
Larynx/subglottis/trachea	2
Subglottis/trachea	1

Sites of Stenosis. Subglottic stenosis alone was found in three. Subglottic and upper tracheal stenosis occurred in one; subglottis, tracheal and laryngeal pathologies in two; and subglottis and laryngeal pathologies in three (Table 1).

The stenotic lumen ranged from no lumen in one patient to 4 mm lumens in three patients. The rest had lumens of 2-3 mm. In the three with accompanying upper tracheal stenosis, the stenotic segments extended down to the tracheal stoma at the third to fourth tracheal ring.

Procedure. The vascularized hyoid interposed in a vertical manner was used in all nine patients. The lumens of the stenotic subglottis and/or upper trachea were augmented. The lateral and posterior stenotic sites were injected with corticosteroids intraoperatively in four patients. One patient each had excision of the posterior and lateral subglottic stenosis and coverage with a buccal mucosal graft and a superior based mucosal flap. Montgomery laryngotracheal stents were placed in five patients and not in four.

Of the five patients with accompanying laryngeal pathologies, three had accompanying laryngofissures with two unilateral arytenoidectomies and two lysis of glottic webs and laryngeal keel placement (Table 2). One patient had

TABLE 2. OPERATIVE PROCEDURE

	No.
Vascularized hyoid interposition	
Subglottis	6
Subglottis/upper trachea	3
Accompanying laryngeal procedure	
Arytenoidectomy	2
Lysis of glottic web and keel placement	2

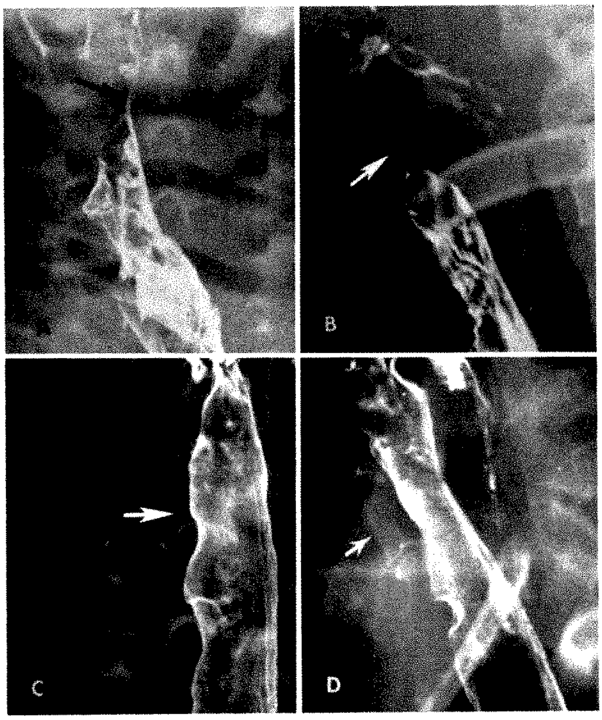

Fig. 4. Patient with subglottic stenosis: contrast laryngotracheograms show stenosis and resultant lumen 31 months after hyoid interposition. A) Preoperative: AP. B) Preoperative: Lateral. C) Postoperative: AP; hyoid bone viable and without resorption. D) Postoperative: Lateral.

a delayed unilateral arytenoidectomy for a belatedly diagnosed bilateral vocal cord paralysis. One patient had moderate laryngeal stenosis without airway or vocal function compromise and no laryngeal procedure was performed.

Decannulation. The vascularized hyoid interposition and necessary accompanying laryngeal procedure were successful (Fig. 4). Eight of the nine patients were decannulated. Only one patient had persistent stenosis. The patient with the persistent stenosis originally had an anterior 50% glottic web, complete subglottic stenosis, and severe upper tracheal stenosis from the first to the fourth tracheal cartilage. The restenosis occurred in the subglottis. The interposed hyoid was used to repair subglottic and upper tracheal stenosis. The glottic web was concomitantly repaired with incision and laryngeal keel placement.

The eight decannulated patients all had adequate voice postoperatively and were all able to breathe and function in a normal fashion. Acute laryngotracheal bronchitis has occurred in some of these patients since the operation and has not compromised the airway.

The resultant lumens were found to be oval in shape, not round (Fig. 5). We estimated the usual result to be 70 to 80% of the normal lumen, but this was adequate for airway maintenance. These patients have follow-ups from 6 to 36 months, with the majority from 12-24 months.

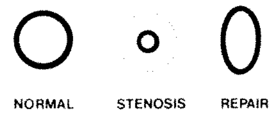

Fig. 5. Lumenal repair: A) Normal subglottic lumen. B) Stenotic lumen. C) Postrepair lumen: not a perfect restitution. Anteroposterior dimensions are less than normal.

Complications. Two patients had minimal wound infections, and minimal tracheal stoma infections occurred in one other. The infections were treated without difficulty.

The major problem has been delayed decannulation secondary to granulation tissue. This occurred in four patients. Infection was felt to be responsible for the granulation tissue in three patients. Two patients had minimal wound infections; one other had purulent peristomal infection. They were all treated successfully with endoscopic removal of the granulation tissue and injection with steroids. The delayed decannulation was from two to seven months versus the nondelayed decannulations of two to four weeks.

One other had delayed decannulation secondary to a previously undiagnosed bilateral vocal cord paralysis at the time of the hyoid interposition. The patient was successfully decannulated after a unilateral arytenoidectomy. This reinforces the necessity to completely evaluate the larynx, subglottis and trachea before performing the surgery.

DISCUSSION

The treatments of subglottic and upper tracheal stenosis are well-described in the literature. Multiple methods are claimed to provide a good success rate. Serial dilatation and awaiting laryngeal growth was successful in congenital subglottic stenosis in the hands of Holinger et al.[5] The present authors have not tried the prolonged stent method of Goode and Shinn.[9] However, in some of our patients, serial dilatation and injection with steroids had been tried without success.

Lumenal augmentation with auricular cartilage,[10] septal cartilage,[12] and other distal sites[11,25] has been reported as being successful by various authors, but requires a separate operative site. The use of the thyroid ala as advocated by Fearon et al[15] is probably useful in chronic subglottic stenosis but is not helpful in subglottic stenosis with upper tracheal stenosis. The thyroid cartilage flap used is frequently not sufficiently long.

Free hyoid versus vascularized hyoid is a logical question. Alonso et al felt that the free hyoid was successful in dogs[24] and in clinical application.[16] The use of free hyoid is technically easier. The authors have tried this method in their canine study. On the other hand, we have shown that a vascularized hyoid is successful in canine studies[1] and in clinical application. The vascularized hyoid, we feel, has the theoretical advantage of less bony resorption, and therefore presents a better opportunity in achieving a lasting adequate lumen. Technically it is slightly more involved, but insures the graft of its own blood supply instead of depending on adjacent vascular ingrowth.

Alonso et al[16] and Ward et al[2] have used the hyoid for laryngeal stenosis as well as subglottic and tracheal stenosis. While none of our reported patients had repairs of laryngeal stenosis by the hyoid interposition, it would have been feasible.

The major problem in our series has been with granulation tissue resulting in delayed decannulation. The predisposing factor causing the granulation tissues appears to be infection. In patients with even minimal purulent material noted at the tracheal stoma, granulation tissue can result. Patients with any purulent material around the tracheal stoma should be treated vigorously with antibiotics, meticulous tracheal stoma care, and frequent tube changes. The granulation tissue can be treated with endoscopic removal and injection with steroids. One of the authors (H. K.) has used the laser with good results in the control of the granulation tissue.

We feel that stent placement is not necessary for moderate stenosis but can be helpful in those with severe stenosis. It is mandatory if lateral and posterior stenotic scar tissues are excised and covered with mucosa or skin grafts.

As the operation only restores and augments the anterior portion, the lateral and posterior stenotic areas are not repaired. Injection of steroids, excision of the scar tissue posteriorly and laterally and coverage with a mucosal flap, buccal mucosal, or split-thickness skin graft have been helpful.

The lumenal restoration with the hyoid is not a perfectly round shape but is an elliptical shape. We have found that the restored lumen is approximately 75% of the normal. Complete restitution is usually not attainable but all patients were markedly improved when one considered that the original lumenal diameter prior to the repair was 3-4 mm at best.

Our present recommendation is that patients with minimal subglottic stenosis be given a trial with dilatation and steroids. If that fails, we recommend the use of lumenal augmentation with the hyoid bone. In patients with less than 2 mm lumen, the success of dilatation and injection of steroids is unlikely; lumenal augmentation will probably be required.

The use of the vascularized hyoid interposition for lumenal augmentation has proved to be a successful and practical technique in our experience.

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AORTIC ARCH ANOMALIES IN ADULT DISORDERS OF DEGLUTITION

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Congenital vascular anomalies of the aortic arch are unusual etiologies of dysphagia in the adult. Swallowing abnormalities associated with compression of the esophagus primarily occur at birth or in the immediate neonatal period. However, as the result of arteriosclerotic vascular disease or aneurysm formation, anomalies which were asymptomatic postnatally may produce dysphagia in the adult. A retrospective analysis of 59 cases with aortic arch anomalies presenting initially in adulthood revealed characteristic clinical signs and symptoms. An aberrant right subclavian artery with left aortic arch was the most frequently encountered abnormality. The embryologic development of each vascular anomaly is described and the value of selective arteriography with contrast esophagography is stressed. Patients with minimal swallowing impairment are treated with dietary management alone. Surgical division of the anomalous artery is indicated only when severe dysphagia is associated with progressive life-threatening anorexia and weight loss.

Congenital vascular anomalies of the aortic arch are unusual etiologies of dysphagia in the adult. Swallowing abnormalities related to vascular compression of the esophagus primarily occur at birth or in the immediate neonatal period. In the infant with tracheoesophageal compression secondary to a vascular ring, cough, inspiratory and expiratory stridor, cyanosis with feeding and recurrent pulmonary infections are the predominant symptoms. Because of the more rigid trachea in the adult, dysphagia is the main symptom of vascular tracheoesophageal compression.

In the majority of instances, aortic arch anomalies remain unrecognized throughout the lifetime of an individual. As a result of aneurysm formation, arteriosclerotic vascular disease and senile changes in the aortic arch and its branches, anomalies which were asymptomatic postnatally may present with dysphagia in the adult.

The primary purpose of this paper is to identify the mode of clinical presentation and discuss the embryological development of those aortic arch anomalies encountered in the adult. In addition, the diagnostic value of selective arteriography with contrast esophagography is stressed. A comparison group of adults with aortic arch anomalies without swallowing dysfunction is examined in order to identify any significant clinical differences.

HISTORY

As early as 1787 a paper was read before the Medical Society of London dealing with an unusual case of obstructed deglutition by David Bayford of Lewes.[1] This was a fascinating account of an unfortunate 62-year-old female with a 20-year history of dysphagia which ultimately progressed to severe anorexia, cachexia and death. Bayford subsequently performed an autopsy and described his findings: "At length, by mere accident I discovered an extraordinary lusus naturae in the disposition of the right subclavian artery. . ."[1] Bayford's term, *dysphagia lusoria* (from lusus naturae — a freak of nature), is still employed to describe the aberrant right subclavian artery. However, it is also loosely applied to dysphagia resulting from other aortic arch anomalies which are by no means less freaks of nature.

Anatomically, the aberrant right subclavian artery was identified earlier by Hunauld in 1735 and by 1899 Holzapfel had collected more than 133 cases.[2,3] Additional aortic arch anomalies were described prior to their recog-

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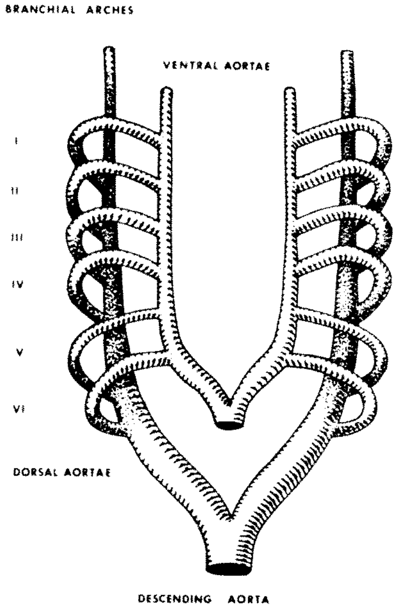

Fig. 1. Primitive aortic arches. Rathke diagram.

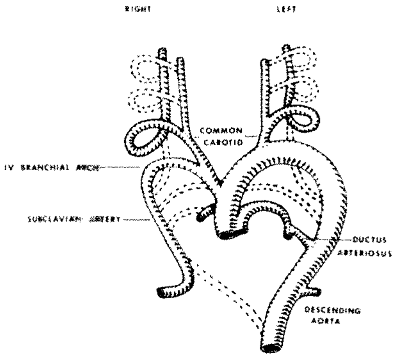

Fig. 2. Aortic arch development. Broken lines refer to arches undergoing regression.

nition as a cause of dysphagia: the double aortic arch by Hommel in 1737,[4] the right aortic arch 1766 by Klinkosch[5] and the left aortic arch with descending aorta by Panus in 1857.[6]

Following Kommerell's roentgenographic description of a single case of aberrant right subclavian artery in 1936, clinical interest in aortic arch anomalies as an etiology of dysphagia increased.[7] Only ten years later Gross of Harvard reported the first surgical correction of aortic arch anomalies for tracheoesophageal compression.[8,9] Presently, surgical treatment of both congenital and adult aortic arch anomalies is common.[10-12]

EMBRYOLOGY

The first major intraembryonic vessels which develop in the three-week embryo are the dorsal aortae, running along the axis of the embryo. As a result of cardiogenic plate rotation and fusion of the ventral aortae to form the aortic sac, the cranial portions of the dorsal aortae become arched and imbedded in the mesenchyme of the branchial arches.[13] The paired dorsal aortae fuse to form a midline descending aorta, while between the ventral and dorsal aortae the six paired aortic arches eventually develop (Fig. 1).

In human development not all arches are present simultaneously. The first and second arches disappear in the 10 mm embryo after the third and fourth branchial arches are established. The fifth arch, as well as the primitive dorsal aorta between the bilateral third and fourth arches, appears and quickly regresses. The sixth arch persists to form the pulmonary artery and ductus arteriosus. Concomitant changes occur in the aortic sac which divides to form separate aortic and pulmonary trunks.[13-15]

The ventral aortic trunk forms the ascending aorta, while the fourth left aortic arch becomes the normal left aortic arch (Fig. 2). The third arch and dorsal aortae cephalad to these arches form the bilateral internal carotid arteries.[13] As an outgrowth of the Rathke diagram and to further explain the development of the aortic arch and its malformations, Edwards' double aortic arch system is applied[14] (Fig. 3). In this primitive double aortic arch which is normal in reptiles, there is an anterior and posterior aortic arch on each side with a ductus arteriosus. The right ductus arteriosus regresses and although theoretically may occur in aortic arch anomalies producing dysphagia, only the left ductus has been anatomically described.

Each aortic arch gives rise to a common carotid artery and subclavian artery. The ventral portions of the sixth branchial arches form the pulmonary arteries and the dorsal segments become the ductus arteriosum. The development of the normal left aortic arch and all aortic arch anomalies may be explained by spe-

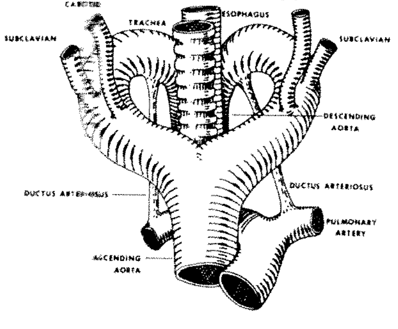

Fig. 3. Primitive double aortic arch.

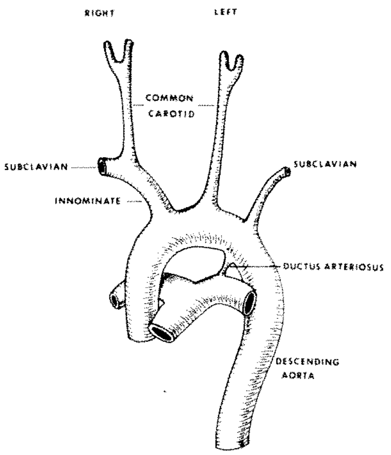

Fig. 4. Normal left aortic arch.

cific interruptions of the primitive double aortic arch.[14]

Theoretically, eight different aortic arch anomalies are capable of producing dysphagia in the adult. These include two forms of double aortic arch (functioning double aortic arch; double aortic arch with partial atresia of one arch), four types of right aortic arch (mirror image branching-rare type; with aberrant left subclavian artery; with aberrant innominate artery; with left descending aorta) and two forms of left aortic arch (with aberrant right subclavian artery; with right descending aorta).

Normal Left Aortic Arch (Fig. 4). The normal left aortic arch develops as a result of interruption of the dorsal segment of the embryonic right posterior arch between the subclavian artery and the descending aorta with regression of the right ductus arteriosus[14] (Figs. 3 and 4). The left aortic arch is a continuation of the ascending aorta, passing anteriorly and to the left of the trachea and esophagus, and descending to the left of the spine. The ductus arteriosus is attached to the inner aspect of the left arch.[16] A barium swallow demonstrates an impression on the left and anterior aspects of the esophagus at T_3-T_4 in the PA and right anterior oblique views respectively.[17] Dysphagia is not associated with the normal left aortic arch. In 70% of patients the successive branches of the aortic arch are the innominate, left common carotid and left subclavian arteries, while 25% of individuals exhibit a common innominate and left common carotid trunk.[16]

Functioning Double Aortic Arch (Fig. 3). The double aortic arch with functioning right and left arches is the most common type of vascular ring producing tracheoesophageal compression in infants.[14,16,18-20] It is uncommon in adults with an incidence in selected autopsy series ranging from 0.011% to 0.017%.[21] As a result of persistence of the primitive double aortic arch, the anterior ascending aorta divides into a right and left arch each giving off a common carotid and subclavian artery. The left anterior arch pursues the course of the normal left aortic arch, passing anteriorly to the trachea and left main bronchus, joining the descending aorta to the left of the esophagus. The right or posterior arch passes over the right main bronchus, turning behind the esophagus and joins the left arch at its junction with the descending aorta, either behind or to the left of the esophagus. The ductus arteriosus inserts into the left arch between its junction with the descending aorta and the origin of the left subclavian artery.[14] A vascular ring is formed with a short tight ductus arteriosus retracting the pulmonary artery dorsally and medially, pushing the anterior wall of the esophagus against the trachea. In addition, the ductus simultaneously pulls the dorsal left arch anteriorly compressing the esophagus.[22]

In the PA view, plain roentgenography of the chest reveals widening of the mediastinum with a right aortic arch and left descending aorta. Esophagography demonstrates bilateral compression defects in the PA projection at variable levels above T_3-T_4 with a posterior indentation in the lateral view.[21] Angiography reveals an ascending aorta dividing into two separate arches, each giving rise to its respective brachiocephalic vessels. Esophagoscopy demonstrates a pulsatile compression posteriorly in the esophagus approximately at T_3-T_4.

Right Aortic Arch with Mirror Image Branching-Rare Type (Fig. 5). The right aortic arch with mirror image branching-rare type is by implication extremely unusual in adults. In general,

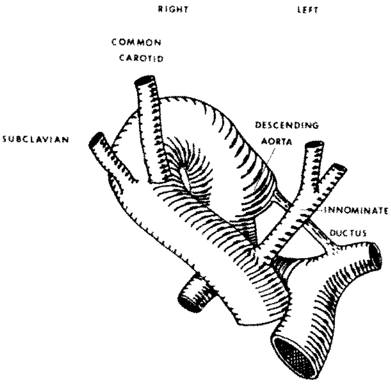

Fig. 5. Right aortic arch with mirror image branching-rare type.

a right aortic arch with left ductus arteriosus is the second most common aortic arch anomaly found in infants; however, this represents the common type with the ductus arteriosus attached to the innominate artery crossing anterior to the trachea.[18,20,23] Its incidence in autopsy series varies from 0.02% to 0.07% and because no retroesophageal component exists, a vascular ring is not formed.[21,24] In addition, the common type is almost always associated with cyanotic heart disease – particularly tetralogy of Fallot and truncus arteriosus.

By contrast, the rare type is unusual and develops from an interruption in the left aortic arch between the ductus arteriosus and subclavian artery with the ductus attached to the descending aorta[16] (Figs. 3 and 5). The right aortic arch passes over the right main bronchus continuing as the descending aorta, the upper portion of which lies to the right of the esophagus and descends to the right of the vertebral column.[14] Roentgenographically, a plain PA view of the chest discloses displacement of the trachea to the left, absence of the left aortic knob with a right aortic arch in the fourth intercostal space, and a right-sided descending aorta.[25,26] The barium swallow demonstrates lateral compression of the esophagus by the right aortic arch in the PA view and marked indentation of the posterior aspect of the esophagus in the lateral projection.[16,26] The left anterior oblique view discloses a triangular shadow in place of the aortic knuckle displacing the esophagus anteriorly and to the left[27] (Fig. 6). Angiography reveals a right descending aorta, coursing cephalically and obliquely to the right of the trachea, and descending sharply to the right of the midline. The first branch of the right aortic arch is the left innominate artery followed by the right common carotid and right subclavian arteries. An aortic diverticulum, which is the remnant of the left posterior arch, is visible projecting from the lateral wall of the upper descending aorta.[16,28] Dysphagia in this anomaly is produced by the ductus arteriosus completing a vascular ring and pulling the aortic diverticulum anteromedially, compressing the esophagus posterolaterally.[29-32]

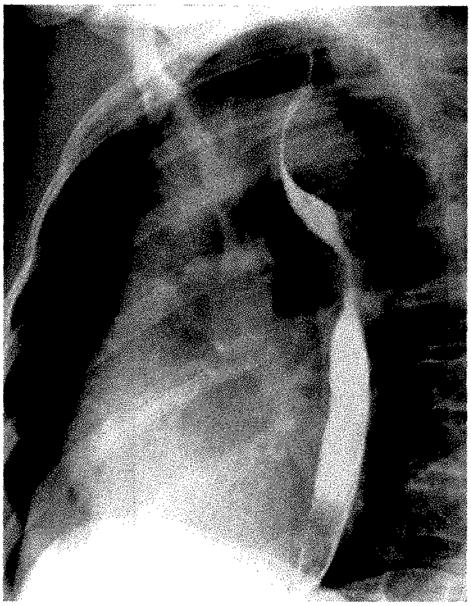

Fig. 6. Right aortic arch with mirror image branching-rare type. Barium swallow- left anterior oblique view: proximal descending aorta indents the esophagus posteriorly.

Right Aortic Arch with Aberrant Left Subclavian Artery (Fig. 7). The right aortic arch with aberrant left subclavian artery is the most common right aortic arch anomaly found in adults with an incidence of 0.1% in selected autopsy series. Only 5% of patients have associated congenital heart disease. It devel-

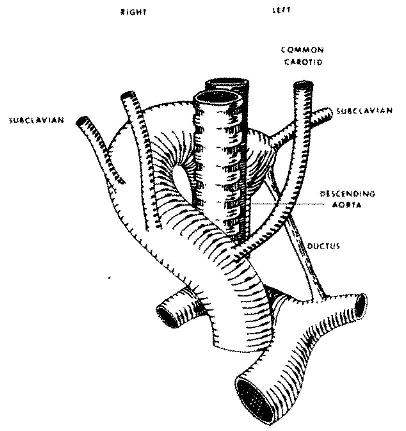

Fig. 7. Right aortic arch with aberrant left subclavian artery.

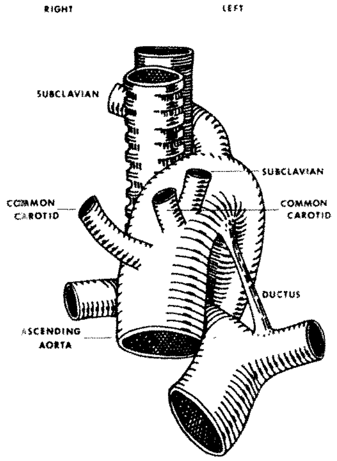

Fig. 8. Left aortic arch with aberrant right subclavian artery.

ops as a result of interruption of the double aortic arch between the left subclavian and common carotid arteries[14] (Figs. 3 and 7). The proximal portion of the left anterior embryonic arch regresses with the left common carotid arising as the first branch of the ascending aorta, while the dorsal portion of the left arch persists as an aortic diverticulum giving rise to the left subclavian artery. The left ductus arteriosus may be attached to either the retroesophageal diverticulum or left subclavian artery completing a vascular ring.[16] The former variation yields a higher incidence of esophageal compression due to anteromedial displacement of the right aortic arch behind the esophagus produced by the tight ductus arteriosus.[21]

A plain PA view of the chest demonstrates a right aortic arch which is smaller and located more superiorly than the normal left aortic arch, indentation of the right side of the trachea, and a shadow to the left of the trachea due to the aortic diverticulum. In the lateral view, the barium swallow discloses a posterior mound-like indentation. A small notch on the left side of the esophagus and oblique filling-defect extending cephalically from right to left just below the aortic arch is seen in the PA view.[16-33] The right anterior oblique projection reveals a deep indentation of the right aortic arch and proximal left subclavian artery in the posterior esophagus. Esophagoscopy discloses either a slit-like opening in the proximal thoracic esophagus or a partial pulsatile compression at the level of the aortic arch.[26, 33] Angiographically, the ascending aorta arises to the right of the trachea and esophagus with the first branch the left common carotid artery followed by the right common carotid, right subclavian and left subclavian arteries.[16]

Left Aortic Arch with Aberrant Right Subclavian Artery (Fig. 8). The left aortic arch with aberrant right subclavian artery is the most common aortic arch anomaly in adults. Its incidence is reported as varying from 0.4% to 2.0% in selected autopsy series.[34-39] Four and four tenths percent to 10% of patients have associated congenital heart disease.[21,40] The anomaly develops from interruption of the right anterior aortic arch between the common carotid and subclavian arteries (Figs. 3 and 8). The right subclavian artery originates from the diverticulum-like remnant of the right posterior arch and passes posteriorly to the esophagus in 80% of patients and between the esophagus and trachea in the remaining cases.[34,41]

The plain PA chest roentgenogram is normal. Rarely, the diverticulum-like origin of the aberrant vessel produces a convex prominence just above the aortic knob simulating a mediastinal tumor. Occasionally, a band-like density is

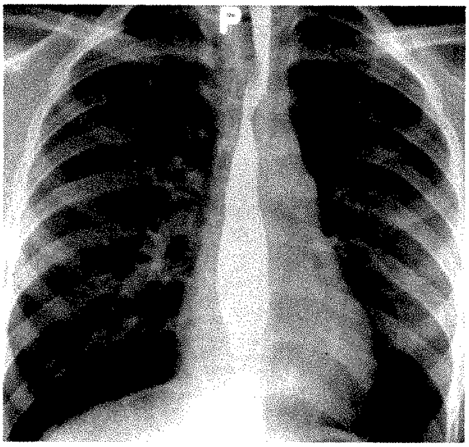

Fig. 9. Left aortic arch with aberrant right subclavian artery. PA view: Barium-filled esophagus reveals an oblique filling-defect extending cephalically between T_3-T_4.

visible crossing the tracheal air column.[16,21,42] In the PA view, the barium swallow discloses an oblique filling-defect extending from below and left cephalically to the right (Fig. 9). The lateral view demonstrates a posterior identation which varies from C_6 to T_4. The left anterior oblique projection provides the most useful diagnostic information, revealing a wedge-shaped impression on the posterior aspect of the esophagus[42] (Fig. 10).

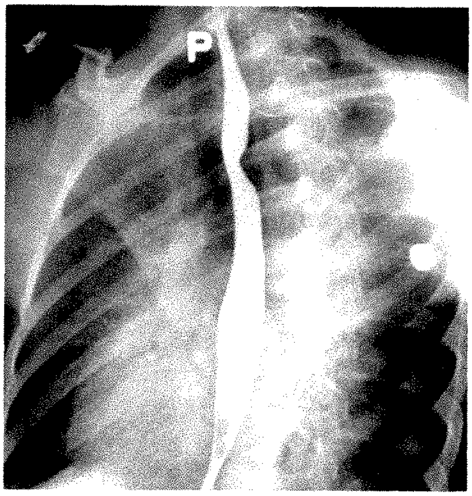

Fig. 10. Left aortic arch with aberrant right subclavian artery. Left anterior oblique view: Note the wedge-shaped impression on the posterior esophagus.

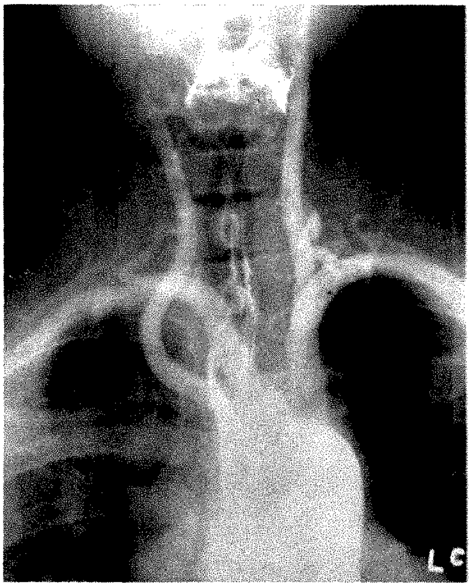

Fig. 11. Left aortic arch with aberrant right subclavian artery. PA view: Note the aberrant vessel crossing the barium-filled esophagus.

Compression of the aberrant vessel with the esophagoscope results in obliteration of the right radial pulse while in the majority of patients posterolateral pulsatile obstruction of the esophagus is observed in the proximal thoracic esophagus.[43,44] Angiography demonstrates a left aortic arch, with the first branch the right common carotid artery followed by the left common carotid, left subclavian and right subclavian artery originating at the junction of the distal arch and upper descending aorta (Fig. 11). An aortic diverticulum may be present at the origin of the right subclavian artery from the upper descending aorta, while in 10% of cases the artery arises from the lower descending aorta.[16,21]

In slightly less than one third of patients, the right and left common carotid arteries arise from a common trunk (i.e., bicaroticus).[45] Additionally, 10% of cases exhibit the two arteries located closer than normal along the left aortic arch. This may prevent the trachea and esophagus from releasing tension created by the abnormal course of the vessel compressing the esophagus.[17,46]

METHODS AND MATERIALS

A retrospective analysis of the English literature from 1794 to 1978 was performed and only those cases with autopsy, roentgenographic or surgical confirmation of an aortic arch anomaly were included. In addition, patient records were reviewed for aortic arch anomalies presenting during the period 1950-1977 at the following hospitals: Hospital of the University of Pennsylvania, Graduate Hospital of the University of Pennsylvania, Presbyterian University of Pennsylvania Medical Center and the Philadelphia General Hospital.

Only adults without a prior history of dysphagia, dyspnea on exertion, stridor or substernal or thoracic pain were included in the study. Patients with congenital heart disease were excluded. In all cases there was no concomitant evidence of either a primary esophageal motility disorder or an extrinsic or intrinsic esophageal neoplasm.

RESULTS

Thirty-six patients with aortic arch anomalies initially presenting with dysphagia in adulthood were identified (Table 1). A left aortic arch with aberrant right subclavian artery was the most frequently encountered anomaly (69.4%).[1,10-12,20,34,46,47-57] Twenty-two and two tenths percent of patients with dysphagia presented with a right aortic arch with aberrant left subclavian artery.[25-28,58] Two adults with a functioning double aortic arch (5.6%) and one with a right aortic arch mirror image branching-rare type (2.8%) were identified among the university-affiliated hospitals.

TABLE 1. AORTIC ARCH ANOMALIES PRODUCING DYSPHAGIA IN THE ADULT

Type	*Number*	
Left aortic arch with aberrant right subclavian artery	25	(69.4%)
Right aortic arch with aberrant left subclavian artery	8	(22.2%)
Right aortic arch, mirror image branching-rare type	1	(2.8%)
Functioning double aortic arch	2	(5.6%)
Total Cases	36	(100.0%)

The average age at diagnosis for this group of patients with dysphagia was 46.5 years with a female/male ratio of 1.6:1 (Table 2). Duration of dysphagia prior to diagnosis averaged 6.5 years with dyspnea on exertion the most frequently associated clinical finding (22%). Seventeen percent exhibited retrosternal or epigastric pain with swallowing while 14% had persistent cough or dysphonia. Only two patients demonstrated upper extremity paresthesias. One third of patients underwent esophagoscopy which disclosed characteristic extrinsic compression of the esophagus at the level of the anomalous vessel. In six patients an aneurysm of the aortic arch anomaly was identified either angiographically or surgically.

TABLE 2. CLINICAL FINDINGS IN PATIENTS WITH AORTIC ARCH ANOMALIES PRODUCING DYSPHAGIA (N = 36)

	Yr	*Patients*
Average age at presentation	46.5	
Sex distribution: female/male ration 1.6:1		
Duration of symptoms prior to therapy	6.5	
Associated clinical findings		
Upper extremity paresthesias		2(5.6%)
Dyspnea on exertion		8(22 %)
Retrosternal or epigastric pain		6(17 %)
Cough or dysphonia		5(14 %)
Aneurysm		6(17 %)

No confirmed cases of double aortic arch with partial atresia of one arch, right aortic arch with left descending aorta, right aortic arch with aberrant innominate artery or left aortic arch with right descending aorta were identified as producing dysphagia in the adult.

A comparison group of 23 patients with aortic arch anomalies initially presenting in adulthood but without dysphagia were analyzed for significant differences (Table 3). The most common anomaly was again the left aortic arch with aberrant right subclavian artery (70%).[12,40,45,59-68] Twenty-six percent demonstrated a right aortic arch with aberrant left subclavian artery, while one patient displayed a double aortic arch with partial atresia of the

TABLE 3. AORTIC ARCH ANOMALIES IN ADULTS WITHOUT DYSPHAGIA

Type	*Number*
Left aortic arch with aberrant right subclavian artery	16 (70%)
Right aortic arch with aberrant left subclavian artery	6 (26%)
Double aortic arch with partial atresia of one arch	1 (4%)
Total Cases	23 (100%)

left arch. There was no statistically significant difference between the two groups with respect to clinical findings except for the occurrence of dysphagia.

It is difficult to evaluate treatment modalities and therapeutic results in this retrospective analysis. Because many cases managed by diet alone or requiring no therapy go unreported, results have no statistical validation. However, in the total sample of 59 patients with confirmed aortic arch anomalies, over half (52.5%) required no therapy or were managed by dietary manipulation alone while the remainder underwent surgical therapy. Twenty-three patients were treated with primary ligation of the anomalous vessel and an additional five patients underwent ligation with reanastamosis and establishment of arterial flow in the distal aberrant artery. The majority of patients were approached via a left lateral thoracotomy (17) while six patients underwent right lateral thoractomy and the remaining five a median sternotomy.

Short-term evaluation for patients managed by diet alone was not available. Of the 15 patients treated surgically for which a minimum of six months follow-up was available, a significant postoperative morbidity and mortality was observed. One third of this group expired either in the immediate postoperative period or within one month of surgery. However, it is noted that these cases occurred early in the various authors' experience and primarily in elderly patients with aneurysms (mean age 66). One third of patients exhibited marked improvement in swallowing function, while two patients developed the subclavian steal syndrome and one peripheral right arm ischemia.

DISCUSSION

Tracheoesophageal compression secondary to an aortic arch anomaly is more commonly observed in the neonate or infant where respiratory symptoms predominate. In adults, the majority of aortic arch anomalies are asymptomatic throughout the lifetime of an individual.[33] As as result of aneurysm formation, arteriosclerotic vascular disease, or loss of elasticity within an aberrant vessel, anomalies which were asymptomatic postnatally may produce dysphagia in the adult. In addition, the tethering effect of the ductus arteriosus which completes a vascular ring and pulls the aberrant artery anteromedially compressing the esophagus posterolaterally accounts for the significant dysphagia which may be produced.

The most common type of aortic arch anomaly producing dysphagia in the adult is the left aortic arch with aberrant right subclavian artery, followed by the right aortic arch with aberrant left subclavian artery and functioning double aortic arch. The present study supports the observation that the right aortic arch with mirror image branching-rare type is extremely uncommon. Theoretical causes of dysphagia in the adult not observed in this study occur primarily in infants and are associated with a high incidence of congenital heart disease: right aortic arch with left descending aorta, double aortic arch with partial atresia of one arch, right aortic arch with aberrant left innominate artery, and left aortic arch with right descending aorta.

Dyspnea on exertion in the group with dysphagia was the most frequently associated clinical finding, presumably due to partial tracheal compression resulting in an additional 14% incidence of persistent cough or dysphonia. Inequality of the radial pulses, though described by other authors, was not identified in this study.[40,47] A comparison group of 23 patients with aortic arch anomalies without dysphagia presenting in the adult, revealed no significant differences except the absence of swallowing dysfunction and a higher incidence of occult superior mediastinal mass subsequently identified as an aneurysm of the aberrant right subclavian artery.

Esophagoscopy was employed in 30% of patients and revealed either a posterior or lateral pulsatile compression varying from C_5 to T_4 which was dependent upon the course of the anomalous artery. However, esophagography and aortic arch angiography are the most important diagnostic techniques in identifying the type of aortic arch anomaly. Surgical division of the anomalous vessel is indicated only when associated with severe progressive anorexia and weight loss as in Bayford's original case. Those types of anomalies amenable to surgical correction in the adult include the right aortic arch with mirror image branching-rare type, the right aortic arch with aberrant left subclavian artery, functioning double aortic arch, and left aortic arch with aberrant right subclavian artery.

Ligation of an aberrant subclavian artery is usually approached via a left lateral thoracotomy. This requires the establishment of continuity of distal pulsatile flow to prevent the development of a subclavian steal syndrome from the ipsilateral vertebral artery and to ameliorate peripheral arm ischemia.[49-51] These problems are avoided either by implantation of the distal subclavian artery in the common carotid artery or by reimplantation end-to-side into the ascending aorta. Careful maintenance of greater than 50% of normal oxygen tension in the lateral sinus as measured via catheter in the superior vena cava will eliminate the concern for postoperative subclavian steal.[63] Finally, aneurysmectomy is indicated especially in those patients with a related history of trauma, severe arteriosclerotic vacular disease, aortitis, or partial obstruction with poststenotic dilatation where sites exist for potential perforation or as a source of thrombus or peripheral emboli.[64]

SUMMARY

Congenital vascular anomalies of the aortic arch are unusual etiologies of dysphagia in the adult. As a result of arteriosclerotic vascular disease or aneurysm formation, anomalies which were asymptomatic postnatally may produce dysphagia in the adult. Thirty-six patients with dysphagia presenting in adulthood were identified. A left aortic arch with aberrant right subclavian artery was the most commonly encountered anomaly, followed by the right aortic arch with aberrant left subclavian artery, functioning double aortic arch and right aortic arch with mirror image branching-rare type. Additional aortic arch anomalies capable of producing dysphagia in the adult were not observed due to their primary occurrence in infants and association with congenital heart disease.

Dyspnea on exertion was the most frequently associated clinical finding along with persistent cough or dysphonia, presumably secondary to partial tracheal compression. A comparison study of 23 patients with aortic arch anomalies without dysphagia presenting in the adult revealed no significant differences except for the absence of swallowing dysfunction.

Patients with minimal swallowing impairment are treated with dietary management alone. Surgical division of the anomalous artery is indicated only when severe dysphagia is associated with progressive life-threatening anorexia and weight loss. The establishment of continuity of distal pulsatile flow is necessary to prevent the development of a subclavian steal syndrome or peripheral ischemia of the extremity.

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TRAUMATICALLY ACQUIRED CONDITIONED DYSPHAGIA IN CHILDREN

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A new diagnosis identifying a nonorganic basis of dysphagia is proposed in relation to behavioral conditioning processes and thereby labeled "conditioned dysphagia" (CD). Literature review of both animal and human studies documents that rapidly acquired and persistent avoidance responses are learned when autonomic functions are contiguous with traumatic physical events. Three case studies with primary diagnoses of TE fistula, congenital heart disease and pseudobulbar palsy demonstrated an association between CD and early childhood incidence of trauma involving the esophagus. Successful treatment was achieved by operant deconditioning therapy. Results of a pilot epidemiological study of 28 postpharyngeal flap surgery children and 47 controls showed significantly higher incidence of mild to moderate CD in the surgery group.

In a comprehensive medical review of the literature, Illingworth[1] found difficulty in isolating the problem of dysphagia from a classificatory diagnostic viewpoint as well as from an etiological perspective. He attributes the difficulty to the partial attention given to the disorder by medical specialties likely to be presented with the problem of dysphagia as a secondary symptom. Illingworth defines dysphagia broadly as the presence of sucking and/or rumination difficulties. He concludes that the literature available on the subject suggests a three factor classification system: 1) gross structural abnormalities, 2) neuromuscular problems, and 3) acute infective conditions. The subject of our paper is to present evidence for a fourth category which identifies "conditioned dysphagia" as it is acquired and maintained through behavioral conditioning processes and is thereby classified as a learned disorder or maladaptive habit.

LITERATURE REVIEW

The conditioning phenomenon of acquired avoidance behavior in response to environmental stimuli has been well-established and the process is cited as either conditioned emotional response (CER)[2] or conditioned suppression[3] in experimental work with animals as well as human subjects. The principles of behavior therapy rest in part upon the view that avoidance responses are, for the most part, adaptive behaviors which enable the organism to avoid aversive stimulation or punishment. When the avoidance response persists long after the probability of presentation of the aversive stimulus is greatly diminshed, the response is considered a fixed maladaptive habit and the organism must be systematically taught to decondition the habit.

Avoidance responses acquired through the pairing of neutral and aversive stimuli, so that a neutral stimulus comes to elicit a conditioned response similar to the "fear" response associated with the aversive stimulation, are said to be classically conditioned responses. These newly acquired responses are manifest by autonomic reactivity or instability, which in turn may serve as a mediator resulting in operant conditioned responses (voluntary central nervous system control). The complete pattern of covert (auto-

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nomic) and overt (CNS) conditioned avoidance responses is known in the conditioning literature as *two-factor theory*[4] and has formed the basis of behavioral deconditioning methodology.[5,6] The theory suggests that autonomic instability is frequently interpreted cognitively as unwarranted fear or anxiety and may serve as a negative drive state in maintaining avoidance or phobic behavior. The secondary gain or alternate sources of reinforcement derived from phobic behavior serves further to fix the habit.

With regard to classically acquired conditioned consummatory avoidance responses associated with visual, auditory and gustatory stimuli, Garcia et al's[7] classical experiment demonstrated that the emergent CER associated with feeding in experimental rats was a function of both elements of temporal contiguity of stimuli and responses, as well as "built-in" conditioning mechanisms. Together, these processes serve to establish a functional link between types of aversive stimulation and coping avoidance responses appropriately designed to ensure survival. Visual and auditory cues associated with an aversive electric shock delivered while eating were therefore found to suppress consummatory responses upon repeated presentation of the cues. On the other hand, taste aversions were produced when the rats were X-irradiated at the time of feeding and did not experience aversion until several hours after feeding. No aversion was found in this condition to the visual and auditory cues occurring at the time of feeding in the absence of electric shock.

Further experimental findings relating to the characteristics of CER implicate developmental and extinction-resistant processes. Early laboratory conditioning work by Pavlovian-influenced American researchers demonstrated the rapidly acquired and fatal withdrawal behavior ("conditioned neurosis") exhibited by infant lambs and goats separated from their mothers when they were administered unavoidable aversive stimulation following visual cues.[8] Gantt[9] documented a case of a laboratory dog, who after brief exposure to aversive conditioning of cardiac responses, produced the same cardiac arrythmia when returning to the laboratory after 13 months of rest. Garb and Stunkard[10] identified the existence of persistent taste aversions in humans, some for as long as 50 years. Eighty-seven percent of the 265 sample subjects reporting taste aversions could trace their taste aversions back to an incidence of gastrointestinal illness associated with the particular gustatory stimulus. Heligman and Hager[11] noted further that taste aversions may be acquired in humans to food consumed before illness, even when the subject knows the illness was not related to the food.

A computer search, coded "functional dysphagia" of the medical and psychological literature of the past decade, located only one therapeutic deconditioning study.[12] An adult woman was treated for chronic dysphagia with successful application of electromyographic (EMG) biofeedback training. One further study in the biofeedback field has been reported by Schuster.[13] Six cases of esophageal reflux were given EMG biofeedback of the lower esophageal sphincter and were taught to monitor and control their ability to maintain a higher ratio of resting sphincter pressure to intragastric pressure. While no specific outcome is reported, Schuster concludes that the voluntary control patients can gain over autonomic functions of this type is "impressive, rapid and with minimal discomfort."

CASE REPORTS

The following three cases were referred for psychological consultation (behavior therapy) for treating chronic dysphagia when all medical and surgical interventions either proved ineffective or were considered irreversible, thereby placing the patient at further risk while prognosis was equivocal regarding the dysphagia. All three children had identifiable medical or anatomical abnormalities in the absence of a neuromuscular or central nervous system dysphagia-related lesion. Each was under five years of age at the time of referral, refused all oral food intake and were consequently fed through fixed gastrostomy tubes. While physical and mental development was delayed secondary to medical hospitalizations, none of the children were diagnosed mentally retarded or severely physically handicapped.

CASE 1

Gregory was born to a 24-year-old gravida 1 after an uncomplicated pregnancy and delivery. The presence of a tracheoesophageal fistula, H type, was identified at one week of age following a barium swallow study. A large amount of barium was aspirated during the study. Subsequent clinical status necessitated permanent tracheotomy and gastrostomy (GT) feedings. At the age of 18 months he underwent a colonic interposition to restore continuity of esophagus and stomach. Postoperatively, gastrostomy feedings were continued because of refusal to take oral feedings. By 2½ years of age he was transferred to a convalescent hospital after repeated efforts to place him with his own or another family failed.

Diagnosis of Conditioned Dysphagia. Repeated instances of medical-surgical trauma involving the upper esophagus and thoracic region could have served as the unconditional aversive stimuli which were contiguous with swallowing reflexes. Once a CER inhibiting the autonomic functioning of swallowing elicited by oral stimulation was established, the gastrostomy feedings prevented secondary reinforcement of oral feedings as occurs in normal children. The absence of the operant or voluntary control of oral feedings was influenced by two factors: a) suppression of autonomic components of swallowing reflexes, followed by, b) removal of the necessity to perform oral feeding for survival, resulting in the minimization of deconditioning effects. Medical institutionalization of the child further contributed to the maintenance of the operant avoidance behavior because no systematic effort was made to decondition the child while on tube feedings. Gregory was receiving biological and social reinforcement with tube feedings instead of oral feedings.

Conditioning Treatment Course. Behavior modification methodology based upon the deconditioning of the maladaptive operant behavior was implemented when Gregory was three years, ten months. While it was clear that he presented many complex problems of delayed development of gustatory and oral hunger mechanisms, the treatment plan focused upon establishing and maintaining operant oral behavior. Not tube feeding the child in an effort to increase motivation to eat orally only resulted in hyperirritability and extreme negativism. Behavioral interventions progressed in three phases:

1. Shaping by positive reinforcement of psychomotor components of oral feeding behavior.

2. Contingency plan making tube feedings contingent upon oral feedings.

3. Massing the learning trials over a 72-hour period.

The inability to control all relevant environmental contingencies and implement the program during all tube feedings in early attempts at deconditioning contributed to a delay in outcome. The decision was therefore made to conduct a massed-trial period with a single therapist (KK) living in with Gregory on the medical ward. Feeding orally was established along with toilet training immediately following this plan. The total time from referral to removal of the GT tube was one year, nine months.

CASE 2

Laura was referred at 12 hours of age because of cardiac anomalies. She was noted to have difficulty swallowing, but no problems sucking. At the age of seven months a pulmonary artery banding was performed. Her postoperative course was fairly unremarkable except for some mild laryngeal edema secondary to intubation. When she was fed after surgery, she had increased difficulty in swallowing, choking and regurgitating. Barium swallow was done, revealing no anatomic obstruction.

Diagnosis of Conditioned Dysphagia. While the medical diagnosis of this child differed from that of Case 1, the acquisition of CER to swallowing was identical and required alternative feeding through gastrostomy. Early respiratory failure, intrusive diagnostic procedures and surgical intervention could each have accounted for the aversive conditioning trials.

Conditioning Treatment Course. She was referred for behavior modification at two years of age. In spite of the presence of both parents and an outpatient status which overcame the institutionalization problem, GT removal after establishing oral feeding was possible only after two years, eight months. Deconditioning therapy, however, was interrupted by long periods of missed appointments because the parents felt secure with continued tube feedings and were reluctant to establish shaping of oral responses. The child was frequently withdrawn from treatment for minor colds or other pediatric ailments. During the later phases of treatment, continuous video feedback of the shaping procedure resulted in rapid gains in self-feeding responses in the absence of choking, vomiting or voluntary rejection of food. Parents were then able to participate actively in the treatment plan and carried out learning trials at home.

CASE 3

Tina was born after a 42-week gestation which was unusual only for the question of maternal polyhydramnios and some evidence of fetal wastage. From the initial neonatal period she had gross difficulty in coordinating her suck and swallow and had repeated episodes of gagging and possible aspiration. There were no neurological or developmental abnormalities found other than the dysphagia problem. Barium swallow, skull x-rays, and EEG were normal, as were a variety of blood and urine tests. Note was made of poor behavioral tolerance of the barium study accompanied by ejecting the barium upward into the nose and mouth. The dysphagia in the absence of gross pathological findings was considered a congenital neurological disorder and diagnosed as probable pseudobulbar palsy. Because of her continued difficulty to feed orally, a gastrostomy was performed at one month of age.

Diagnosis of Conditioned Dysphagia. Tina was referred at one year, five months when the above clinical evaluation failed to result in identification of a lesion to account for the chronic dysphagia. In contrast to the first two cases, Tina did not only refuse to eat, but also did not swallow excess saliva or mucus drainage from the nasal passages. The fluids either drained from her nose or resulted in continuous drooling. It was assumed possible that the nasal regurgitation of food and liquid contributed to the appearance of the CER. A structural anomaly of the palate contributed to the nasal regurgitation mechanism. This case also presented evidence of the possible contribution of intrusive esophageal diagnostic procedures which might have served to fix the CER, resulting in the chronic conditioned dysphagia.

Conditioning Treatment Course. Using similar deconditioning procedures described in the first two cases, Tina began eating sufficient quantities of food to permit removal of the GT tube after one year of outpatient treatment. While the parents were cooperative, a younger sibling and the mother's work schedule made tube feedings less troublesome for the family than consistent efforts at deconditioning. At termination of conditioning therapy, the patient was not returned by the parents for GT removal for another 13 months.

DISCUSSION

Identification of Populations At-risk for Conditioned Dysphagia. The possibility that any form of physical trauma to the upper chest, throat, mouth and nasal region could provide necessary grounds for conditioned dysphagia in children suggests the need for epidemiological study of a wide variety of at-risk groups. Systematic investigation of incidence of disorder, as a follow-up to the extreme problems presented by the clinical cases discussed in this paper, has been undertaken. To date a population of children having undergone pharyngeal flap surgery were carefully surveyed for postoperative feeding problems.[14] The experimental group consisted of 28 children who had surgery within one year of the investigation. A feeding survey was administered to one parent by raters blind to the clinical status. Results were compared with nearest-age siblings controls (n = 22) and a control sample and their sibs (n = 25) matched for age and sex. The average age of all children ranged from eight to nine years. Results showed that the pharyngeal flap group obtained significantly more behavioral feeding problems than all other groups. The problems included eating too slowly, not finishing meals, eating only small quantities of food with each mouthful, and requiring physical assistance (usually cutting gummy food into small pieces). This characteristic pattern of eating avoidance behaviors is consistent with a diagnosis of conditioned dysphagia, although less clinically severe than the cases reported in the preceding section. No differences emerged among the groups in relation to food preferences or taste aversions. It would therefore appear that the Garcia effect, i.e., avoidance associated with contiguous aversive stimulation, was replicated. The supression of consummatory responses is redefined in humans as conditioned dysphagia. Taste aversions do not readily appear in humans in the absence of delayed gastrointestinal symptoms.

It is estimated that 40% of the pharyngeal flap group could have benefited from postoperative conditioning therapy and that the mild-to-moderately-severe form of conditioned dysphagia existed as an undiagnosed and unsystematically treated problem. The problem was usually associated by the parent with nonmedical causation and almost all parents were not seeking professional help.

Other at-risk groups currently under study include a follow-up of former TE fistula cases, a cohort of barium swallow cases, cases requiring intrusive interventions for treatment of foreign object ingestion, and cases requiring dental surgery and orthodontic procedures in children. Patients with psychiatric conditions, including forcible sexual acts (fellatio), may also be at-risk for the occurrence of extinction-resistant conditioned dysphagia.

CONCLUSIONS

The diagnosis of conditioned dysphagia is proposed in cases heretofore unrecognized and untreated in the absence of identifiable lesions. Evidence is based upon contemporary conditioning literature, three severe clinical cases treated successfully with deconditioning therapy, and preliminary findings of a particular at-risk group. The incidence of conditioned dysphagia in cases traumatized by medical, surgical or intrusive diagnostic procedures involving the esophagus is estimated at 40%, based upon a group of children with postpharyngeal flap surgery. Etiological considerations and symptomatic sequelae in identifying the disorder include:

1. Early incidence (birth - five years) of physical trauma involving the esophagus and contiguous with the autonomic swallowing reflex.

2. Severe nature of trauma.

3. Persistent dysphagia after removal of original trauma or successful surgical repair in the absence of a CNS or autonomic nervous system lesion, infection or gross anatomical anomaly.

4. Absence of systematic posttraumatic parental or professional efforts at deconditioning.

5. Characteristic eating avoidance pattern including taking small quantities with each mouthful, eating too slowly, not finishing meals and requiring physical assistance in carefully cutting down all large pieces of chewy foods.

6. Responsive to deconditioning therapy, including shaping new eating behaviors and desensitization of fear of swallowing.

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NATIONAL HEARING ASSOCIATION

The National Hearing Association, a newly formed, not-for-profit foundation dedicated to the cause of cure and prevention of deafness, opened its national headquarters offices at 1010 Jorie Boulevard (Suite 308), Oak Brook, IL 60521 on February 3, 1978. Some of the country's leading otologists and interested business and community leaders are emphasizing the fact that funds available to support research for the cure and prevention of deafness are far less than funds devoted to other handicaps that affect a much smaller percentage of the population. The National Hearing Association is dedicated to correcting this deficency in research funding.

Mr. M. A. Self is Chairman, George E. Shambaugh, Jr., MD is President and J. William Wright, Jr., MD is 1st Vice-President of the Association.

Those interested in helping the National Hearing Association by becoming active members and/or assisting in chapter development, fund raising, and other activities are urged to write: National Hearing Association, 1010 Jorie Boulevard (Suite 308), Oak Brook, IL 60521.

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UNSUSPECTED FOREIGN BODIES OF THE AERODIGESTIVE TRACT

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The well-known tendency for children to place loose objects in their months not infrequently leads to the entrapment of foreign bodies in the aerodigestive tract. With prompt and adequate removal few complications occur. However, when the foreign body goes undetected or is neglected the patient may develop dysphagia, pneumonia, failure to thrive, lung or mediastinal abscesses, bronchopulmonary or bronchoesophageal fistulas, or erosion of major vessels. Fifteen cases of retained foreign bodies were identified in a chart review between 1971 and 1977 at the Children's Hospital of Philadelphia, calling attention to the problems of aerodigestive foreign bodies of prolonged duration. Early and late complications are discussed and early diagnosis and endoscopic removal emphasized.

Children often seem inherently compelled to place loose objects in their mouths. Many times this leads to the swallowing or aspiration of a foreign body. Foreign body aspiration is one of the leading causes of accidental death in children under six years of age.[1] In most instances ingested foreign material passes through the gastrointestinal tract without incident. When foreign material is aspirated, however, initial gagging, coughing, and choking occur. Fortunately, the majority of patients present with these historical signs, suggesting that aspiration has occurred.[2,3] Some patients, however, may be first observed in an asymptomatic period that often follows the initial symptoms and allows the tracheobronchial and esophageal foreign material to go unsuspected.

The course of the illness after a foreign body lodges in the air and food passages depends on the characteristics of the foreign body and its length of stay.[4] Foreign material that is unsuspected or neglected may lead to changes resulting in chronic pulmonary disease and catastrophic paraesophageal complications. Bronchiectasis may necessitate resection of lung parenchyma; esophageal foreign bodies may erode into major vessels, resulting in exsanguination.

The purpose of this paper is to call attention to the problems caused by undetected foreign bodies in the tracheobronchial tree and esophagus. The complications will be discussed, emphasizing the need for early endoscopy to prevent irreversible disease. In a retrospective chart review, 15 patients with unsuspected foreign bodies were found at the Children's Hospital of Philadelphia between 1971 and 1977. No cases in adults were found in the same time period at the University of Pennsylvania Hospital. Five cases are summarized to illustrate the elusive clinical problems that may arise when an unsuspected foreign body is present in the aerodigestive tract.

FOREIGN BODY CASE REPORTS

Case 1 (Tracheobronchial). A six-year-old female was admitted through the emergency room with an eight-week history of recurrent pneumonia and bronchitis and a one-day history of hemoptysis. About eight weeks prior to admission the patient had multiple tooth extractions under general anesthesia. In the postoperative period the patient suffered from what was diagnosed as croup, which responded to conservative therapy. Over the ensuing weeks she developed two episodes of pneumonia that responded to antibiotics. At the time of ad-

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mission she had a persistent cough and bronchitis and was being treated with bronchodilators. Physical examination of the chest showed decreased tactile fremitus on the right with diffuse rhonchi and inspiratory wheezes. Chest x-ray revealed a foreign body in the right bronchus. At bronchoscopy a tooth fragment was removed from the right bronchus.

Case 2 (Tracheobronchial). An 11-year-old male was brought to the emergency room because of abdominal pain of two weeks' duration. He denied all symptoms of chest pain, dyspnea, fever, chills, or cough. His mother reported that several bouts of hemoptysis had occurred one year prior to this admission, but had not recurred. Chest x-rays demonstrated a hat pin in the lower left lobe. Bronchoscopy was performed and a rusted pin was removed.

Case 3 (Esophageal). A 15-month-old male was transferred to Children's Hospital with a safety pin in his esophagus. The patient had been seen one week prior to admission by a local physician for a persistent cough and fever of two weeks' duration. A course of antibiotics was unsuccessful in eliminating symptoms. When an admission chest x-ray revealed an open safety pin, the patient was transferred to Children's Hospital. The patient's temperature was 38 C, the lungs had diffuse rhonchi, and the WBC was 31,500. Chest x-ray showed an open safety pin in the esophagus and soft tissue density in the mediastinum. At esophagoscopy a corroded safety pin, which broke with handling, was removed without difficulty. The patient was then prepared for a thoracotomy. In the area of the soft tissue density, a cavity was encountered which contained pus and blood. After suctioning the cavity clear, a massive hemorrhage ensued. In spite of intensive efforts by the general surgery and cardiothoracic teams, the cardiopulmonary resuscitation was unsuccessful. Autopsy showed an abscess cavity communicating with both the esophagus and subclavian artery.

Case 4. (Tracheobronchial). An eight-year-old male was well until age six years, when he developed recurrent respiratory tract infections, fever, and cough. He was diagnosed as having right lower lobe bronchiectasis, for which he underwent a right lower lobectomy and eventually a right middle lobectomy. Over the following two years he continued to have a cough productive of yellow sputum stained with blood, which did not clear with antibiotic therapy. A chest x-ray and bronchogram showed left lower lobe pneumonia and bronchiectasis. He had diffuse rhonchi and rales bilaterally. Sputum culture grew alpha hemolytic streptococci and Neisseria. White blood count was 8,300 and immune deficiency work-up was negative.

At bronchoscopy pus extruded from the left lower lobe, and the mucosa was edematous and friable. A piece of bone was removed from the left lower lobe. Postoperatively the patient was placed on postural drainage and chest physical therapy.

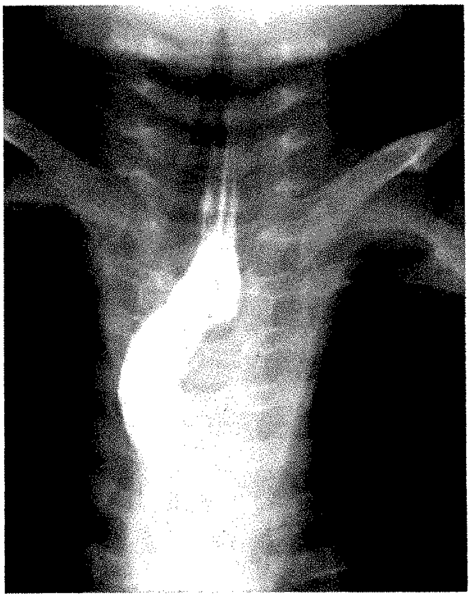

Fig. 1. Barium swallow showing deviated esophagus around nutshell.

Case 5 (Esophageal). A ten-month-old female was admitted with a three-week history of hoarseness and wheezing. The symptoms developed during an upper respiratory infection and were accompanied by fever, cough and rhinorrhea. Expiratory wheezing and dyspnea had progressively worsened. On admission she was hoarse and her cry was weak. There was no history of foreign body ingestion or dysphagia.

Physical examination revealed a well-nourished child with hoarseness and a weak cry. There was no fever. The chest had an increased A-P diameter and mild intercostal retractions were present. There was prolongation of expiration and diffuse wheezing bilaterally.

Chest x-rays showed deviation of the trachea to the right, compression of the left main bronchus and hyperaeration bilaterally. Fluoroscopy showed left vocal cord paralysis which was confirmed by direct laryngoscopy. Barium swallow showed the esophagus to be deviated to the right by an extrinsic mass (Fig. 1).

The mass was caused by a paraesophageal foreign body (a nutshell) found at exploratory thoracotomy. The nutshell was surrounded by acute and chronic inflammation. Three days after thoracotomy, massive hemoptysis required a second thoracotomy at which time a tracheoesophageal and aorticoesophageal fistulae were repaired. Four days later a massive esophageal bleed could not be controlled, and the patient died.

DISCUSSION

Foreign bodies of the tracheobronchial tree may remain unsuspected for long periods of time. The longest period among the cases reviewed in this series was 22 months. However, Denney et al report removing a pipe stem that had been trapped in the bronchial tree for 25 years.[5] The long sojourn may be due to an absence of historical information suggesting aspiration. A negative history is present in 15% of the cases of foreign body aspiration.[3] Also, as stated by Jackson and Jackson in 1950, an asymptomatic period between the time of aspiration and the development of late symptoms can lead to an error in diagnosis.[6]

Foreign bodies in the tracheobronchial tree tend to lodge on the right side because the right main bronchus has a greater diameter and lesser angle of deviation from the trachea. Also the carina is slightly to the left and a greater volume of air enters the right lung. Five of the 11 bronchial foreign bodies in our series were on the left, which may have contributed to their being unsuspected.

Long-standing foreign bodies of the esophagus are not as common (four in this series) but as in cases of respiratory foreign bodies, the patients may have no history suggesting ingestion.[2] The initial symptoms of gagging, coughing, and choking may soon subside or go unnoticed by parents. An asymptomatic period may follow that is prolonged by a diet of fluids and soft foods that easily pass the partial obstruction. The diet may also be spontaneously selected, minimizing any symptoms and maintaining nutrition in those patients under two years of age who are in the high risk group (Case 3).

Physiologically and roentgenographically the esophagus has five areas of constriction where foreign bodies may become lodged. The most important areas are the cricopharyngeal narrowing at C_6 and the hiatal narrowing at T_{10} and T_{11} where 95% of foreign bodies come to rest. Other sites of narrowing are the thoracic inlet T_1, the aortic arch T_4, and the tracheal bifurcation T_6 where the left main bronchus crosses the esophagus.[7]

Foreign bodies in the aerodigestive tract that go undetected or are neglected may lead to late complications associated with infection. Eleven patients with bronchial and four patients with esophageal foreign bodies were found at the Children's Hospital of Philadelphia in a six-year period. The symptoms are not characteristic of a foreign body and present as the symptoms of superimposed disease. Three of the four patients with esophageal unsuspected or neglected foreign bodies presented with respiratory symptoms including hoarseness.

Radiographic changes may occur immediately following aspiration or may become apparent later as infection persists.[4] The natural history of foreign bodies in the lung was demonstrated by Weinberg in 1937 with vegetable material placed in the bronchi of rabbits. He found emphysema in 20 minutes, atelectasis and infection in 6 to 42 hours, and bronchiectasis developed in 14 to 58 days.[8] This indicates the importance of early bronchoscopic removal of foreign material with aspiration of the tracheobronchial tree to avoid foreign body bronchiectasis and possible need for surgical resection (Case 4). J. S. Linton suggests that simple removal of the foreign body may be sufficient to reverse chronic pulmonary changes, thereby avoiding the need to resect pulmonary parenchyma.[9]

Unsuspected foreign bodies in the esophagus seem to be tolerated less well than bronchial foreign bodies and lead to serious complications earlier.[6] The complications are frequently reflected in the respiratory system, but may be elusive presentations such as failure to thrive.[10] The foreign body may obstruct the trachea by impinging on the thin, cartilage-free wall between the trachea and esophagus. Recurrent pneumonia may occur from aspiration resulting from esophageal obstruction or tracheoesophageal fistula formation.[6] Later the unsuspected foreign body may erode the esophagus, causing mediastinal abscess, vocal cord paralysis, and erosion of major vessels with massive hemorrhage.

It is apparent that endoscopy (bronchoscopy and esophagoscopy) is important in diagnosis of foreign bodies in the aerodigestive tract to prevent complications. Nonradiopaque materials may be missed on x-ray, and only the effects of superimposed infection may be seen. Even contrast studies (bronchography and esophagram) may not demonstrate the offender.[11] Kim et al suggest that bronchoscopy be performed in patients presenting with cough, sneeze, and decreased entry of air into the lungs during seasons when upper respiratory infections are few.[3] The cases presented here would indicate that bronchoscopy and esophagoscopy should be considered for children with unexplained or progressive respiratory symptoms to rule out a foreign body.

Avoiding the potential effects of unsuspected foreign bodies starts with preventive measures in the home. Withholding hard foods like nuts and vegetables from children under the age of three years and examining chopped foods for bones is essential. Small objects should be kept out of reach of young children who explore their environment with their mouths.

When a patient reaches the office, a careful history with specific questions about foreign bodies in the mouth may be revealing, but the initial episode may have gone unnoticed, and both bronchial and esophageal foreign bodies may be asymptomatic for a period of time following ingestion. Lateral neck and chest x-rays with inspiratory and expiratory views may be helpful in any patient with cough, wheezing, or dyspnea. An esophagram may demonstrate a foreign body but is not always conclusive.

Bronchoscopy and esophagoscopy offering direct visualization and a means for extraction should be considered an early part of the diagnosis and treatment of foreign bodies of the aerodigestive tract. Early removal may prevent infectious complications, avoiding chronic pulmonary disease that may later require extirpative surgery, or catastrophic complications from erosion of paraesophageal structures.

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CASE FOR PNEUMATIC DILATATION IN ACHALASIA

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A standardized method of performing pneumatic dilatation for the treatment of achalasia is described. Twenty-five patients were treated in this manner and 80% had excellent results. There was minimal morbidity and no mortality. Pneumatic dilatation is recommended as the primary procedure for achalasia as it is a simple and safe procedure which avoids unnecessary surgery. Local topical anesthesia, rather than general, is utilized and hospitalization time is two days, rather than the 14 days required following surgery. The Heller operation can be performed when pneumatic dilatation is unsuccessful.

Achalasia is a neuromuscular disturbance of swallowing, of unknown etiology. It has been recognized since 1674 when Thomas Willis, cited in Ellis and Olsen,[1] detailed its clinical presentation in a classic paper. He recognized lower esophageal obstruction as a causative factor and used a whalebone as a dilator. Dilatation, in one form or another, has been a principle of treatment since that time.

There are currently two acceptable modes of therapy for achalasia: a surgical approach, using a modified Heller cardiomyotomy, or dilatation using a pneumatic or hydrostatic technique. There are proponents of both modalities and controversy exists as to which is the better. This report presents the case for pneumatic dilatation.

METHODS AND MATERIALS

Achalasia patients frequently have large residues of food and liquids in a chronically obstructed and dilated esophagus. Hence a clear liquid diet should be taken two days prior to admission, and the esophagus thoroughly irrigated with an Ewald stomach evacuator upon admission. The irrigation is repeated on the morning of the dilatation. An empty esophagus decreases the risk of aspiration, and in the unlikely event of perforation, minimizes mediastinal contamination. A recent barium swallow study should be available, and is useful as a guide to the passage of the dilator, particularly in late cases, where tortuosity exists.

Premedication is given one hour prior to dilatation. This should contain an anticholinergic to counteract the bradycardia which frequently accompanies the procedure. Scopolamine 0.3 mg and Demerol® 50 mg IM are adequate, appropriately adjusted for age and weight.

Prior to the dilatation, esophagoscopy is carried out, using the flexible, fiberoptic, end-viewing scope. To minimize the possibility of aspirating any residual liquid in the esophagus, this is most safely performed in the semi-sitting position. Esophagitis, benign stricture and malignancy are carefully looked for and excluded. In typical achalasia, the scope will frequently "drop" into the stomach, after some mild resistance is overcome. If any difficulty in introducing the scope into the stomach is encountered, Hurst mercury weighted dilators are passed under fluoroscopy, up to size 34 F.

The Mosher pneumatic dilator consists of an inflatable rubber covered cloth bag, which contains barium strips, visible under fluoroscopy. The flexible distal tip, 33 F in diameter, contains a 5 cm long spring section. The inflation and gauge system connect to the graduated tube. A flexible staff is provided and used as a stent to lend some rigidity to and facilitate the passage of the dilator.

The patient is placed in the supine position with a slightly reversed Trendelenberg tilt This elevation of the head helps prevent uncomfortable pooling of saliva in the back of the patient's throat, and possible aspiration The operator stands at the patient's head and a nurse, controlling suction apparatus, keeps the patient's mouth empty of saliva during the procedure. The flexible staff is well-lubricated before it is inserted into the dilator tubing. This allows ease of withdrawal of the staff, once the dilator is positioned.

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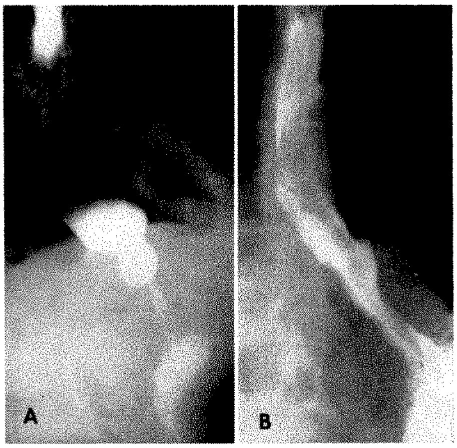

Fig. 1. Eighty-one-year-old female with long history of achalasia. Patient was being maintained on intravenous fluids, unable to swallow any food. A) Barium swallow roentgenogram demonstrates nearly complete occlusion at cardia with marked widening of esophagus. Stomach is markedly diminished in size. B) Following pneumatic dilatation cardia is widely patent, barium flows freely into stomach.

Fluoroscopy is an essential part of the technique, ensuring safe passage of the dilator and accurate positioning of the inflatable bag. The dilator is inserted in similar fashion to passing a Hurst dilator. The flexible staff is used to guide the distal metal tip into the stomach, and then withdrawn. The inflatable bag, seen on the fluoroscope screen, is positioned half above and half below the diaphragm. It is moved until the impression made by the tight esophagogastric junction lies at its midpoint. This can be tested by injecting a small amount of air into the bag, and observing the indentation site.

The bag is then inflated slowly to 1.38 kg/sq cm pressure, and held at that pressure for five minutes. During this period it is normal for the patient to experience pain of moderate severity of a deep, retrosternal nature. It is important to realize that the actual pressure applied to the bag is irrelevant once the maximum diameter is attained, since the cloth bag has a fixed dilatable diameter, beyond which it will not distend. It is only necessary that the bag distend maximally, and this should be checked prior to use. The position of the bag is checked each minute, to ensure that it has not slipped up into the esophagus or down into the stomach. Fluoroscopy reveals a gradual straightening in the balloon, as the dilatation proceeds. It is often necessary to instill air under further increased pressure, in order to erase the indentation in the bag. The distended bag is left in place five minutes because it has been observed that in every instance the bag is fully distended by the end of that period of time.

After five minutes, the bag is withdrawn and inspected. A successful dilatation results in rupture of the muscle fibers and is usually accompanied by blood on the bag.

Chest x-rays are taken immediately and at three hours, and examined for signs of esophageal perforation. If both x-rays are normal and there are no clinical signs of an esophageal tear (such as tachycardia or severe retrosternal pain), and as soon as the local anesthetic effects have worn off, the patient may drink clear liquids. The patient frequently notices immediate relief from predilatation dysphagia. Solid foods are taken the following day, and a repeat barium swallow roentgenogram done to gauge changes in the esophagogastric junction. When the procedure has been successful, the tapered beak-like deformity, typically seen on the roentgenogram prior to dilatation, will be gone, and marked widening of the cardia noted (Figs. 1 and 2). Barium passes freely into the stomach and frequently the diameter of the esophagus has decreased markedly.

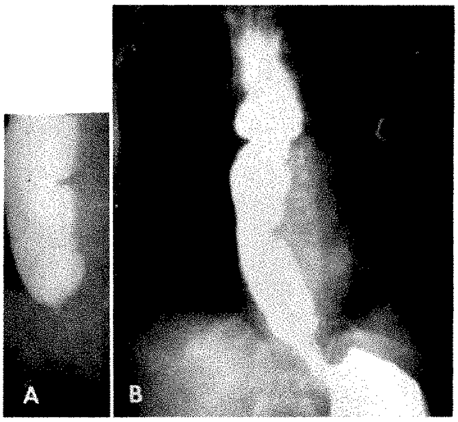

Fig. 2. Advanced achalasia with frequent vomiting and marked impairment in the ability to swallow food. A) Barium swallow roentgenogram demonstrates total obstruction at cardia with retention of barium in esophagus. B) Patent cardia following pneumatic dilatation with free flow of barium into stomach.

RESULTS

Between 1970 and 1977, 25 patients underwent pneumatic dilatation as the primary procedure for achalasia. The diagnosis was made on the history and barium swallow x-ray examination, and confirmed by motility study. Esophagoscopy was performed in each case.

There were ten males and 15 females. The age range was from 29 to 81, with an average of 54 years.

Patients were contacted by telephone whenever possible, and asked to grade the success of their treatment as follows: excellent: completely asymptomatic as regards swallowing; good: good response to dilatation, but noting occasional "sticking" of food; and poor: no better or frequent episodes of "sticking."

Follow-up varied from one month to eight years, with an average of 28 months. Using the above grades, 20 had an excellent response, 1 a good response, and 4 a poor response. Of the four poor responses, one patient was managing, but had frequent episodes of food sticking at the cardia, and three had undergone subsequent Heller operations.

In all the 21 successful dilatations, immediate relief from dysphagia occurred and return to a normal diet was possible. A marked gain in weight was the rule.

There were no complications of mediastinitis, perforation or hemorrhage. All patients had a postdilatation barium swallow roentgenogram and were discharged one or two days following the dilatation.

It was not possible to correlate the change in the barium swallow roentgenogram in every case with the success of the procedure. A review of the roentgenograms revealed a marked change in the configuration of the esophagogastric junction in 17 cases. This consisted of a widening in caliber, with disappearance of the "beaked" deformity and free flow of barium into the stomach. In many instances, the esophagus diminished in diameter after successful dilatation. In eight cases, there was only a very slight change in the esophagogastric junction, and yet in over half of these, there was a good to excellent result. Conversely, in two patients where a marked change did occur on barium swallow, the result was poor.

In two of the four poor results, the dilatation was repeated on a second admission, again with no clinical improvement. In both of these cases, the barium swallow had shown little change after the initial procedure. Both subsequently underwent Heller procedures.

DISCUSSION

The largest experience with achalasia has been reported at the Mayo Clinic (2,364 patients up to 1967). The results of treatment using hydrostatic dilatation technique, were published in 1970.[2] They reported 60-70% good to excellent results with 0.5% mortality. However, the two deaths which occurred were unrelated to the dilatation. There was a 2.4% incidence of rupture of the distal esophagus, requiring operation, with no mortality. It should be noted that fluoroscopic control was not used. If the initial dilatation was unsuccessful, they noted that the patient was much less likely to benefit from additional dilatations. Three or more dilatations increased the number of good results from 60% to 70%. The results of cardiomyotomy were published in 1969.[1] This surgical approach gave a 94% excellent response, with 0.3% mortality and minimal morbidity. They concluded that a cardiomyotomy was indicated as the primary treatment of choice.

Kurlander et al[3] in a long-term study of 62 patients, reported 84% good results using pneumatic dilatation, with zero mortality. Morbidity was minor, and included hemorrhage, chest pain and fever. In an uncontrolled, retrospective comparison, Yon and Christensen[4] noted an 85% good result from myotomy, and a 40% good response to pneumatic dilatation. Van Trappen et al[5] reported 77% excellent results with pneumatic dilatation.

It would appear that purely in terms of the percent of patients attaining symptomatic relief, the Heller procedure may be slightly superior to dilatation. There are, however, other considerations. In Yon and Christensen's[4] series, 25% of the patients undergoing cardiomyotomy suffered from postoperative reflux. Kurlander et al[3] reported no reflux after pneumatic dilatation, as judged by symptomatic heartburn. The incidence of reflux as judged radiographically after myotomy, was 30-52%.[6] Jekler et al[7] quote a 30% incidence of postcardiomyotomy esophagitis. Ellis[8] maintains that if the myotomy procedure is carried out according to the rigid criteria he outlines, reflux esophagitis is not a problem. He quotes a 1.1% incidence in his series.

Reflux esophagitis is only one of the problems associated with a Heller procedure. Thoracotomy carries with it the risk of postoperative pulmonary complications, in addition to the usual anesthetic morbidity and mortality. Incisional pain remains a significant cause of morbidity, and should not be dismissed lightly. Hospitalization lasts to two weeks, and disability persists another two to four weeks.

CONCLUSIONS

Pneumatic dilatation for the treatment of achalasia is a safe procedure with minimum mortality and morbidity; it is effective in 80% of patients treated, and hence avoids unnecessary surgery in the great majority. It is rapidly performed under local topical anesthesia, avoiding the possible complications of a general anesthetic, requires minimal hospitalization time, and has no residual disability.

An advantage of the pneumatic method over the hydrostatic procedure, is that in the latter, the amount of pressure applied must be carefully controlled during the dilatation. In the former, the maximal dilatable diameter of the bag, despite increasing pressure, is effective treatment and is a safeguard against esophageal perforation.

The authors believe that a second dilatation is warranted if symptoms recur after an initial success with the procedure, only if the postdilatation barium swallow shows persistence of the beaked deformity without widened caliber of the esophagogastric junction. No more than two unsuccessful dilatations are indicated.

When dilatation does not restore normal swallowing ability, the Heller operation should be performed. Additional indications for surgery are perforation of the esophagus during dilatation and failure to complete an attempted dilatation. The latter is most likely to occur in the sigmoid esophagus of tertiary achalasia. Others recommend surgery as the initial procedure for children under 12 years of age.[9]

SUMMARY

Pneumatic dilatation of the cardia is a safe and effective treatment for achalasia, and is recommended as the initial procedure of choice. This conclusion is based on an evaluation of 25 patients who underwent pneumatic dilatation with a Mosher bag as primary treatment for achalasia, between 1970 and 1977. The results were excellent in 80% of patients, with minimal morbidity and no mortality. Important details that enhance the safety of the technique are emphasized. Cardiomyotomy (Heller operation), with its attendant pulmonary complications and incisional pain, is unnecessary in 80% of achalasia patients.

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FUNCTIONAL DISEASES OF THE ESOPHAGUS: ROLE OF ENDOSCOPY

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The use of endoscopic procedures in the evaluation of primary motor disorders, or functional diseases, of the esophagus is filled with both risks and benefits. Since both flexible and open-tube esophagoscopy carry a significant risk factor, it is necessary to have a clear concept of the indications and value of endoscopy in the management of functional diseases of the esophagus. A review of the literature reveals very little documentation on the value of endoscopy in diagnosing esophageal functional diseases other than Zenker's diverticulum and achalasia. Based on the current literature and the experience of the authors, observations and recommendations concerning the role of endoscopy in functional diseases of the esophagus are presented. These are: 1) In Phase I or upper esophageal sphincter dysfunctions, endoscopy contributes little to their understanding, is difficult to perform, and may be hazardous. In this group, esophagoscopy should be reserved for indications beyond the dysfunction itself. If endoscopy has to be performed, open-tube esophagoscopy should be performed by an experienced endoscopist. 2) In functional diseases of the esophageal body or Phase II dysfunction, endoscopy is frequently valuable. In spastic disorders, it helps to differentiate between primary spasm of neuromuscular origin and spasm secondary to esophagitis or an obstructive process. In scleroderma and pulsion diverticulum, endoscopy helps to identify such unsuspected complications as esophagitis, hiatal hernia, and carcinoma. 3) In Phase III or lower esophageal sphincter dysfunctions, endoscopic examination is essential both to rule out organic lesions that simulate functional disorders, and to determine the presence and extent of esophagitis.

Investigative procedures commonly used in the diagnosis and management of the primary motor disorders of the esophagus are esophageal fluoroscopy and motility studies. When information obtained by these procedures is insufficient, endoscopy is frequently employed. In some specific motor disorders of the esophagus, like Zenker's diverticulum and achalasia, the role of esophagoscopy is well defined. However, there is very little documented literature that deals with the value of endoscopy in other functional diseases. This review will attempt to define both the risks and benefits of esophagoscopy in the common esophageal functional disorders.

RISK OF ESOPHAGOSCOPY

The risk of esophagoscopy is small but significant. Schiller has reported 26 perforations in 25,563 flexible endoscopic examinations,[1] or approximately one perforation in every 1,000 examinations. The risk of perforation with rigid or open-tube endoscopy is much greater. In a review of Mayo Clinic experience, 30 perforations were reported in 3,696 patients (0.8%) examined with the rigid esophagoscope.[2] Patients with functional diseases of the esophagus may be more susceptible to injury because of altered physiology and anatomy. Therefore, patients with primary motor disorders of the esophagus should be carefully screened prior to esophageal endoscopic examination.

DISORDERS OF MOTOR FUNCTION

Before disorders in the motor function[3] of the esophagus are discussed, the normal physiology will be reviewed. The normal-functioning esophagus provides a highly complex mechanism for the transmission of a bolus of food from the pharynx to the stomach. This esophageal deglutition is an involuntary act that occurs in three phases. The conscious act of swallowing sets the stage

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for the first phase of esophageal deglutition. A reciprocal relaxation of the upper esophageal sphincter allows the bolus to enter the body of the esophagus. Normally, the upper sphincter acts as a one-way valve and remains closed except during deglutition. In the second phase of the swallow mechanism, the bolus that has entered the body of the esophagus is propagated toward the lower esophageal sphincter by well-coordinated primary and secondary peristaltic waves. The third phase consists of a reciprocal relaxation of the lower esophageal sphincter which allows the bolus to enter the stomach. The lower esophageal sphincter also functions as a one-way valve and prevents gastroesophageal reflux.

The underlying etiological factor in functional diseases of the esophagus is an abnormality of any of the three phases of esophageal deglutition. In the upper esophageal sphincter phase (Phase I), the most common abnormalities are: a) impairment of reciprocal relaxation due to either hypertonia or incoordination; and b) incompetence of the upper esophageal sphincter which allows reflux into the pharynx.

In the second phase, the dysfunctions may be: a) partial or complete absence of peristaltic waves, whereby the bolus has to propagate primarily by gravity; and, b) presence of nonperistaltic tertiary contractions. These two dysfunctions may occur either alone or, more frequently, together.

In the third phase of deglutition, the dysfunctions may be: a) impairment of reciprocal relaxation due to either hypertonia (hypertensive lower esophageal sphincter) or incoordination whereby the sphincter fails to relax with the approaching peristaltic wave; and b) incompetence whereby the sphincter loses its one-way valvular function.

Some of these dysfunctions may be temporary in nature and may cause few symptoms. Persistence of these dysfunctions may lead to specific disease entities which are broadly termed functional diseases. Therefore, a functional disease of the esophagus can be defined as a primary abnormality of the motor physiology involving any of the three phases of esophageal deglutition. Secondary structural and anatomical changes may become the hallmark of the disease entity (e.g., pharyngoesophageal diverticulum).

ROLE OF ENDOSCOPY IN FUNCTIONAL DISEASES

Phase I or Disorders of the Upper Esophageal Sphincter. Functional diseases involving the upper esophageal sphincter or the first phase of deglutition include: a) cricopharyngeal dysphagia in which underlying dysfunction is an incoordination or failure of the esophageal sphincter to relax before a bolus of food;[4] b) incompetence of the upper esophageal sphincter in which the contents of the esophagus constantly reflux into pharynx or the nasopharynx, and may predispose to aspiration; and c) pharyngoesophageal diverticulum in which the underlying pathology is also an impairment of reciprocal relaxation of the upper esophageal sphincter due to either incoordination or hypertonia. The presence of an unrelaxed or spastic upper esophageal sphincter raises the pressure in the pharynx during a swallow which leads to diverticulum formation at a potential area of weakness (Killian's dehiscence).[5] Each of these entities can be recognized during esophagographic studies.

Esophagoscopic examination in this group poses a hazard. The flexible endoscope is usually introduced as a blind intubation through the upper esophageal sphincter assisted by the patient's own swallow. In Phase I functional diseases, this particular aspect of the swallow mechanism is impaired. Therefore, the introduction of a flexible endoscope may be difficult and may lead to serious pharyngoesophageal injury.

Dysfunctions of the upper esophageal sphincter also increase the risk of rigid esophagoscopy. The observations of others,[4,6,8] and our experience, have demonstrated that the information obtained by endoscopic examination in this group of patients is usually not significant. While there are rare cases of carcinoma in Zenker's diverticulum reported, the incidence is too small to justify routine endoscopy in these patients.[8,9]

Summarily, in Phase I functional diseases, diagnostic esophagoscopy contributes little new information, is technically difficult, and may be hazardous. Esophagoscopy should be reserved for patients with indications beyond the dysfunction itself. Flexible esophagoscopy is contraindicated.[7] When an additional indication is present, open-tube esophagoscopy should be performed by an experienced endoscopist using a flexible guide to identify the esophageal lumen.

Phase II or Disorders of the Esophageal Body. Functional diseases involving the esophageal body, or Phase II of deglutition, include diffuse esophageal spasm, scleroderma, and pulsion diverticulum.

Diffuse esophageal spasm is a primary neuromuscular disorder in which the underlying motor abnormality is a dominance of nonpropagative tertiary contractions replacing propagative swallow waves. This results in substernal dysphagia, and frequently there is severe or disabling pain. Inflammatory processes in the esophagus, such as reflux esophagitis, also trigger tertiary contractions. Often these contractions are not distinguishable from primary spasm by esophagography or esophageal manometry.

It is important to differentiate primary diffuse spasm from spasm secondary to esophagitis or obstruction in order to initiate effective management. Primary esophageal spasm responds to therapy with smooth muscle relaxants such as nitrites while they have little or no effect on secondary spasm.[10] A precise diagnosis can be established by an endoscopic examination.

Scleroderma has been included in this group because motor abnormalities frequently occur in the esophagus before any structural changes are noted in the esophagus or elsewhere. The underlying pathology in scleroderma is a progressive disruption of the motor activity which leads to a total absence of esophageal motor function. The diagnosis can usually be made by esophagography and confirmed by esophageal motility studies. Therefore, endoscopy is not necessary to establish the diagnosis of uncomplicated scleroderma. However, both an associated hiatal hernia and esophagitis occur in about 50% of the patients. Endoscopic examination is essential to identify the presence and degree of these complications.

In pulsion diverticulum in the body of the esophagus, the underlying abnormality is a marked increase in the intraluminal pressure caused by tertiary contractions. This diagnosis is easily established by radiography. However, other conditions are associated with pulsion diverticulum. In a group of 160 patients with epiphrenic diverticulum reported from Mayo Clinic, 33% of the patients had a hiatal hernia and esophagitis, and 25% had diffuse esophageal spasm. Other associated conditions included carcinoma and achalasia.[11] Therefore, endoscopic examination is essential to clearly define the nature and severity of these associated conditions.

The risk of endoscopy in Phase II functional diseases is low, especially if the flexible endoscope is used. Endoscopy helps in differentiating between primary esophageal spasm and spasm secondary to esophagitis or other organic causes. It also reveals the nature and severity of associated lesions or complications in pulsion diverticulum and scleroderma. This information obtained by esophagoscopy is helpful in the management of these patients. Therefore, in Phase II functional disorders, esophagoscopy is frequently necessary. Flexible endoscopy is the recommended method.

Phase III or Disorder of the Lower Esophageal Sphincter. The common functional diseases that involve Phase III of the swallow mechanism are: a) achalasia; b) hypertensive lower esophageal sphincter; and, c) incompetence of the lower esophageal sphincter.

Achalasia represents both Phase II and Phase III dysfunctions. The Phase II abnormality relates to esophageal peristalsis which varies in degree from disorganized contractions to total loss of peristalsis. The Phase III dysfunction is associated with a loss of reciprocal relaxation of the lower esophageal sphincter. Together, these two dysfunctions cause the failure of the esophagus to empty. As a result, the esophagus gradually becomes distended. Differential diagnosis should always consider the fact that carcinoma of the distal esophagus or gastric cardia may simulate achalasia. Esophageal carcinoma is known to occur in greater frequency in patients with long-standing achalasia.[12] Therefore, endoscopic examination of the esophagus is essential in patients with suspected achalasia, especially when symptoms are of short duration.

In a hypertensive gastroesophageal sphincter, the underlying dysfunction is smooth muscle spasm. The most frequent clinical manifestation is painful swallowing localized to the subxyphoid region.[12] This clinical entity can be identified by radiography and manometry. However, endoscopic confirmation is essential since the narrowing noted by fluoroscopy may represent either spasm secondary to inflammation, a stricture of inflammatory origin, or neoplasm.

Incompetence of the lower esophageal sphincter that occurs in the absence of a hiatal hernia should be regarded as a functional disorder. The value of endoscopy in determining the extent of esophagitis and other sequelae in this group of patients has been well-established. Esophagoscopy is also useful in detecting small hiatal hernias that escape radiologic detection.

In each of the examples of Phase III functional diseases, endoscopy should be routinely performed as an adjunct to fluoroscopic and manometric studies.

CONCLUSIONS

Flexible or open-tube esophagoscopy carries a significant risk factor. Therefore, it is necessary to have a clear concept of the indications and value of endoscopy in the management of functional diseases of the esophagus. The following observations are based on the current literature and our experience: a) In Phase I or upper esophageal sphincter dysfunctions, endoscopy contributes little to their understanding, is difficult to perform, and may be hazardous. In this group, esophagoscopy should be reserved for indications beyond the dysfunction itself. If endoscopy has to be performed, open-tube esophagoscopy should be performed by an experienced endoscopist. b) In functional diseases of the esophageal body or Phase II dysfunctions, endoscopy is frequently valuable. In spastic disorders, it helps to differentiate between primary spasm of neuromuscular origin and spasm secondary to esophagitis or an obstructive process. In scleroderma and pulsion diverticulum, endoscopy helps to identify such unsuspected complications as esophagitis, hiatal hernia, and carcinoma. c) In Phase III or lower esophageal sphincter dysfunctions, endoscopic examination is essential both to rule out organic lesions that simulate functional disorders, and to determine the presence and extent of esophagitis.

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A 16-minute color presentation with sound, Functional Diseases of the Esophagus: Role of Endoscopy, has been prepared by the authors for the Veterans Administration Center for Endoscopic Programs. It is available on U-matic videotape cassettes by intra-VA library loan; or on film and U-matic cassettes by purchase from the National Audiovisual Center, Washington, D. C.

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THE DEAFNESS RESEARCH FOUNDATION

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ULTRAVIOLET-FLUORESCENCE BRONCHOSCOPY IN EARLY DETECTION OF BRONCHOGENIC CARCINOMA

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The still unsatisfactory prognosis of bronchogenic carcinoma prompted the search for possibilities of better early and detailed diagnosis. This led us to the idea of UV-fluorescence bronchoscopy. The patient inhales 5 ml of an aqueous 5% solution of fluorescein, together with a β_2 stimulator, 10-15 minutes before the bronchoscopy, by means of a pressure inhaler. While the normal mucous membrane cleanses itself by virtue of ciliary action (secretions containing fluorescein are expectorated or drawn off during the bronchoscopy), carcinoma, carcinomatous lymphangiosis, superficial tumor infiltrations and nonciliated metaplasias are stained. These places fluoresce in UV light, even when they cannot be observed with the naked eye or with an optical system. In this way, they are made visible for directed biopsy. Malignant changes not discernible by means of the methods hitherto employed can thus be diagnosed and sites determined with greater accuracy for proposed resection.

Bronchogenic carcinoma is the most frequent disease whose diagnosis the doctor has to come to grips with by means of endoscopy. Thus, the study of a five-year period at the University Hospital of Zürich[1] has shown that of 2098 patients who were subjected to bronchoscopy, 901 came for examination on account of suspected bronchogenic carcinoma. It was possible to evaluate 704 of the cases statistically, and in 365 of the cases, bronchogenic carcinoma was diagnosed immediately or in the further course of the disease. These carcinoma cases were picked up in all degrees of advancement and given appropriate types of treatment. The unhappy result was the cure of only 14 patients (barely 4%) with a survival period of five years, which provided the stimulus for undertaking the present work.

Intrabronchial central carcinoma cases (47%) (this figure and the figures which follow relate to the evaluation series mentioned above) present no problems in diagnosis. Also in the 16% of cases of peripheral carcinoma, diagnosis with the flexible instruments and the peripheral brush, suction and tissue biopsy methods has been much improved. With extramural tumors (16%) or microscopically small mural tumors, and with mucous membrane invasions invisible to the naked eye (21%), the situation is difficult.

The evaluation of the mucous membrane central to a visible tumor is also of importance. It has to supply guidance to the surgeon concerning the area for resection. Thirty-two percent of our cases were operated, and the only method open to us was the routine biopsy of the proximal, macroscopically unchanged, large carinae. Directed removal of tissue samples was not possible.

For our better understanding of fine differences in the mucous membrane, we experimented with light of different wavelengths for the endobronchial illumination. These experiments showed[2] that blue light gave increased contrast between yellowish tissue changes, such as mucous membrane nodules, metaplasias, hyper- and parakeratoses and the red mucous membrane. Further experiments were planned, using UV light.

In analogy with work of various authors who marked bronchial, intestinal and oral secretions, as well as vaginal smears, intravitally and postmortem, with fluorescing substances, and exam-

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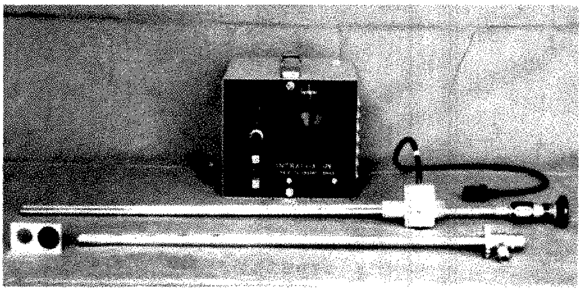

Fig. 1. UV light source with modified optical quartz fiber bundle, combined with the Hopkins optical system to form a single unit, and fitted into the Storz Universal Bronchoscope.

ined the samples outside the body in UV light,[3-9] fluorescing substances were sought with which bronchogenic carcinomata could be stained and made visible in UV light. Tetracycline, which is most commonly used, was not included in our experiments, since from the experience of the authors quoted, this method stipulates several days preliminary treatment before the bronchoscopy is carried out.

Dr. Olsen (Mayo Clinic) drew my attention to the experiments which he carried out with Dr. Lipson and coworkers in 1960.[10-12] They succeeded in staining bronchial tumors with hematoporphyrin administered intravenously. In UV light, these tumors could be seen as fluorescing areas in the bronchial tree.

In the search for a suitable UV light source, I came across an industrial appliance* which was adapted to fit the Storz Universal Bronchoscope with a modified optical quartz fiber bundle (Fig. 1).

Preliminary Experiments. For a start, the same method was followed as had been used with success in the Mayo Clinic. Hematoporphyrin was, of course, not obtainable from the trade, but had to be prepared in accordance with the directions of the Mayo Clinic. None of the experiments with this substance gave any fluorescence whatever, even when intrabronchial tumors were definitely present. It was eventually discovered that our hematoporphyrin itself did not fluoresce, and this shortcoming could not be resolved even after reference back to the Mayo Clinic. It was necessary to seek a different marking substance.

Other intravenously administered substances which might have been secreted in the bronchial tree, as for instance, lactoflavin, gave no positive results. After this, attempts were made to mark the surface by getting the patient to inhale a fluorescein solution. We began, in analogy with the fluorescence technique of the ophthalmologists, with a 1% solution of fluorescein. After numerous failures, positive results were achieved by increasing the concentration of the fluorescein and increasing the intensity of the UV light within the bronchial tree; many experiments in vitro were needed for this purpose.

METHODS AND MATERIALS

A patient suspected from clinical or x-ray examination of having a carcinoma, inhales a 5% aqueous solution of fluorescein + sodium 10-15 minutes before the bronchoscopy. Five milliliters of the solution, together with a β_2-stimulator such as, for instance, five drops of Ventolin®, are administered by means of a pressure inhalation appliance. The bronchoscopy is carried out in a darkened room using normal light and UV light alternately. Any secretion containing fluorescein which may be remaining on the walls of the bronchial tree, is carefully removed by suction. Care must be taken not to cause any bleeding, since this would hide any fluorescence in the region covered by the blood.

RESULTS

We have established from 14 cases where the mucous membrane was nor-

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*Messrs Volpi AG, Urdorf, Switzerland. The acquisition of this appliance was subsidized by the Foundation for Scientific Research of the University of Zürich.

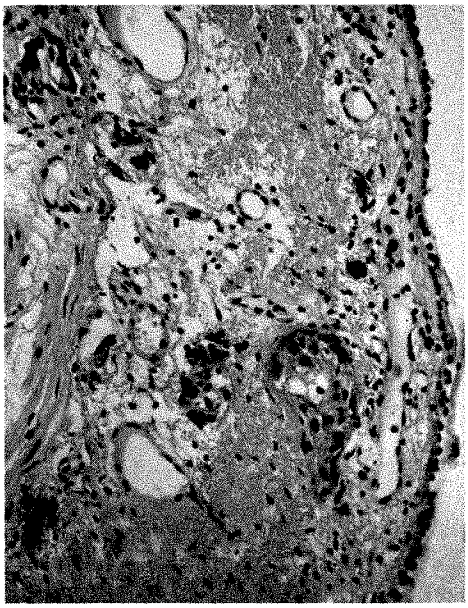

Fig. 2. Macroscopically unchanged bronchial mucous membrane which fluoresced under bronchoscopy in UV light after inhalation of fluorescein. The case is one of carcinomatous lymphangiosis.

mal or was affected by inflammation, that this produces no fluorescence. The layer of mucous membrane covering which has absorbed the fluorescein is transported away by ciliary action, and the secretion is expectorated by the time the examination takes place or is sucked off during the bronchoscopy. Sixteen cases where macroscopic examination had given reason to suspect carcinoma showed a green-yellow fluorescence. The biopsy confirmed the carcinoma diagnosis. Two cases identified by biopsy as carcinoma did not show fluorescence as they were covered by fresh blood.

We see, therefore, that fluorescein adds on to the surface: it is either absorbed by the surface mucus, or it settles on nonciliated areas. While the ciliated sections of mucous membrane cleanse themselves or are cleansed by the suction, the nonciliated areas remain stained, since the fluorescein adheres so firmly that it cannot be sucked off. Carcinomata with their greatly changed surfaces remain stained. It is of course important that they should not be covered with blood.

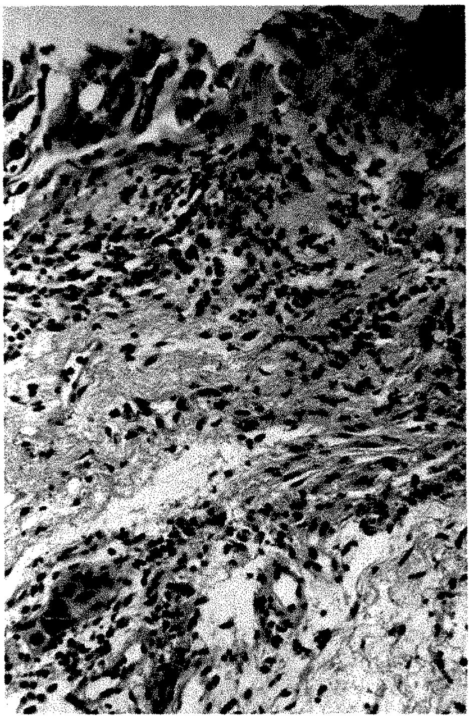

Fig. 3. Fluorescing, macroscopically unsuspicious mucous membrane showing carcinoma invasion.

CASE REPORTS

Three cases which are especially noteworthy are discussed.

Case 1. A 64-year-old male with a hemorrhagic pericarditis, who was suspected from x-ray examination of having a carcinoma in the hilus of the left lung, was sent for bronchoscopy. Examination revealed a rigid, walled-round, drawn-up, left main bronchus. Macroscopically, and from observation by means of the Hopkins optical system, however, the mucous membrane showed no suspicious neoplastic changes. On the other hand, under UV lighting, a fluorescent network appeared, covering the whole of the left main bronchus. Biopsy of one of the fluorescent areas yielded a diagnosis of a carcinomatous lymphangiosis (Fig. 2).

Case 2. The following case is similar to Case 1. This 46-year-old male gave indication of a suspected tumor on the hilus of the right lung. Here again, bronchoscopy showed no visible tumor changes, but only a slight deformation of the lumen in the region of the right upper lobe outlet. On the upper lobe carina, a localized area of mucous membrane showed fluorescence, and this was subjected to a bi-

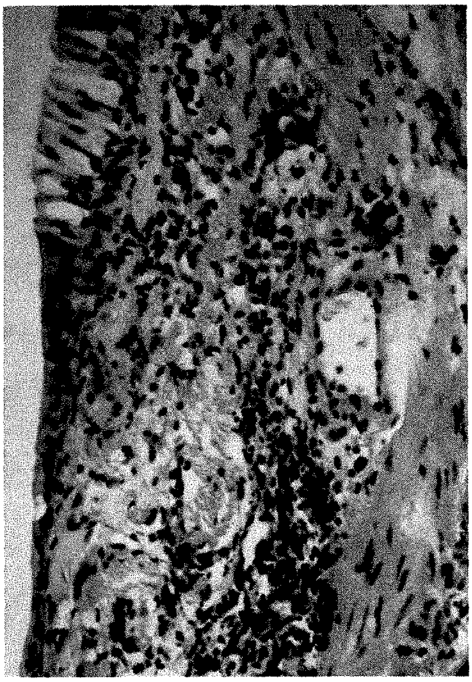

Fig. 4. Fluorescing, macroscopically unsuspicious mucous membrane with a nonciliated pavement epithelium metaplasia.

opsy. The histological examination stated: tumor infiltration into the mucous membrane (Fig. 3).

In these two cases, we are concerned with a carcinomatous lymphangiosis and with tumor infiltration into the mucous membrane which could not be seen by either the naked eye or the Hopkins optical system. Only the fluorescence gave any indication of the region to be examined by biopsy.

Case 3. The patient was a 62-year-old male, suspected, as a result of x-ray examination, of having a central bronchogenic carcinoma; he was examined on the right hand side. Bronchoscopy showed no suspicious tumor elements within the right bronchial tree, however, and no fluorescence appeared on the right. On the other hand, a strip of mucous membrane in the region of the left upper lobe outlet, whose macroscopic appearance was not conspicuous, showed fluorescence. Biopsy indicated that it was a case of a nonciliated mucous membrane metaplasia (Fig. 4). The suspected carcinoma was not confirmed in the subsequent course of the disease.

CONCLUSIONS

Bronchogenic carcinomata can be marked by means of a pressure inhalation of fluorescein solution. In UV light, these changes can be identified as fluorescent areas. Even changes in the mucous membrane due to carcinomatous lymphangiosis or to a tumor infiltration, which are not distinguishable with the naked eye or by means of the Hopkins optical system, give rise to fluorescence. Areas of mucous membrane which have lost their covering of cilia due to a metaplasia also give rise to fluorescence, however. Directed biopsies of fluorescing areas in the bronchial tree may therefore lead to a histological diagnosis of changes in the mucous membrane which have not been detected macroscopically. The extent of spread from the center, of a carcinoma in the mucous membrane, can also be determined much more precisely; that is to say, it is possible to provide the surgeon with more exact details concerning the area for resection. The recidivity ratio following operations can thus be reduced.

The method is simple. The apparatus of Messrs. Volpi is easy to handle. The UV light source described is also being replaced shortly by a model of higher intensity, which is, however, only little larger than the old one. The additional time required is slight. The patient only has to be prepared a short time earlier for the bronchoscopy, since the inhalation, which should, of course, be finished 10-15 minutes before the examination, takes up about ten minutes. The examination itself takes some five to ten minutes longer than usual, since the large bronchial tubes have to be examined with and without UV light, and possibly also a second time after sucking off secretion.

I am aware that the number of examinations is still very small at the present time. The provisional results are, however, encouraging. A more extensive series of examinations is to be started shortly, in accordance with a joint plan, in the ENT clinics of Zürich, Lausanne, and St. Gallen, so that more experience may be accumulated. Other fluorescent substances may possibly also need to be tested, or the method may need to be modified.

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OTOLARYNGIC PATHOLOGY TRAINING PROGRAM

A training program on otolaryngic pathology, presented by the Armed Forces Institute of Pathology (AFIP) in conjunction with the Committee on Otolaryngic Pathology, AAOO, is currently being offered at the Department of Otolaryngic Pathology, AFIP. The course covers both temporal bone pathology as well as surgical pathology of the head and neck area.

Requirements are flexible but preference is given to residents and practitioners in Otolaryngology and Pathology, both military and civilian, who wish to expand their knowledge of ENT pathology. The course, for which there is no charge, is designed to be given quarterly, beginning in January, April, July and October; however, consideration will be given to those seeking shorter training periods.

Requests for course applications should be directed to: The Director, Armed Forces Institute of Pathology, ATTN: AFIP-EDZ, Washington, DC 20306.

Ann Otol 87:1978

EFFECT OF TOPICAL ANESTHETICS ON CILIARY ACTIVITY OF CHICKEN EMBRYO TRACHEAL ORGAN CULTURES

STUDY USING TOTAL IMMERSION AND INTRATRACHEAL INJECTION

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Because of conflicting reports concerning the effect of topical anesthetics on cilia, testing of four different agents was undertaken. The agents were hexylcaine 5% (Cyclaine®), tetracaine 2% (Pontocaine®), cocaine 5% and 10%, and lidocaine 4% (Xylocaine®). Tracheas were removed from 19 to 20 day old chicken embryos. Ciliary activity was graded as to extent and vigor. Two methods of testing were used. In the first, dilutions of each agent were made, and tracheal rings were placed in the wells of microtiter plates and completely covered with the test drug. In the second method of testing, 0.8 ml of the test drug was injected in vivo into the exposed trachea of the embryo. In immersion testing, cilia stopping effect (CSE) in tracheal rings was noted in all drug dilutions tested within 1 to 20 minutes. When the drug was injected directly into the trachea, a complete CSE was noted the next day in the rings from the tetracine and hexylcaine injected tracheas. Three days following in vivo transtracheal injection of lidocaine and cocaine, ciliary activity in these and the control rings was similar. Although cilia did not tolerate total immersion in any of the agents tested, ciliary activity in tracheas injected with lidocaine and cocaine did not differ significantly from the control tracheal rings. Physicians who use topical anesthetics should be aware of this.

Anesthetic agents are frequently used topically on nasal and tracheal mucosal surfaces. Although potential toxicity for cilia has been recognized for these agents, studies have presented conflicting information concerning this toxicity.[1-5] Because our previous studies in organ cultures revealed ciliary damage produced by mucolytic agents[6] and topical decongestants,[7] it seemed appropriate to test other topical agents. Four different anesthetic agents were studied in the chicken embryo tracheal organ culture system.[8] The testing took two forms: in one, ciliary activity was observed after total in vitro immersion in a test drug. In the other, ciliary activity was observed in vitro after in vivo transtracheal injection of the test drug.

METHODS AND MATERIALS

Topical Anesthetic Agents. Four different anesthetic agents were tested: hexylcaine 5% (Cyclaine®), tetracaine 2% (Pontocaine®), cocaine 5% and 10%, and lidocaine 4% (Xylocaine®). The pH of each of these agents was: lidocaine 6.45, tetracaine 4.63, cocaine 5.62, and hexylcaine 6.0. Dilutions of each drug were made by using Eagles basal medium (BME) with 0.05 M N-hydroxy-ethyl piperazine-N'-2-ethanesulfonic acid (HEPES) buffer.

Organ Culture Preparation. The method of organ culture preparation has been previously described.[6-8] In brief, a midline incision was made in the necks of 19 to 20 day old chicken embryos. The tracheas were exposed, removed, cut into ring sections 0.5-1.0 mm thick, and placed in screwtop 16 x 125 mm glass tubes containing 1.0 ml HEPES BME.

The tracheal rings adhered to the side of the tubes 2-5 cm from the bottom. The rings in the tubes were incubated at 37 C on a standard roller drum, one revolution per five minutes. The ciliary activity was graded as to extent of cilia in the ring and the vigor of ciliary activity.

In Vivo Injection of Anesthetic Agents into Chicken Embryo Tracheas. The tracheas of 19 to 20 day old chicken embryos were exposed by a midline incision. A syringe with a No. 2[illegible] needle was used to instill 0.8 ml of the test anesthetic agent into the trachea just below the cricoid. HEPES BME and distilled water were instilled into the tracheas of control em-

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Presented at the meeting of the American Broncho-Esophagological Association, Palm Beach, Florida, April 24-25, 1978.

TABLE 1. EFFECT OF HEXYLCAINE ON CILIARY ACTIVITY OF CHICKEN EMBRYO TRACHEAL ORGAN CULTURES OBSERVED IN MICROTITER WELLS

Hexylcaine Solutions	*% Ciliary Activity by Duration of Exposure* 0 min	2 min	5 min	10 min	20 min
5.0%	100	0	0	0	0
2.5%	100	0	0	0	0
1.0%	98	25	18	11	0
0.5%	98	28	16	25	0
Control fluid	100	100	100	100	100

bryos in the same manner. The trachea was immediately removed and processed as described above. For each drug, ten ring sections were observed.

In Vitro Test of Anesthetic Agents With Chicken Embryo Tracheal Rings. Dilutions of each of the test drugs were made and each experiment was done on two separate occasions. Five tracheal rings were utilized for each trial. Rings were placed into microtiter plate wells,[*] covered with the test drug, and the plate covered to prevent evaporation. The rings were continuously observed and graded using an inverted microscope. When ciliary activity was markedly diminished or had ceased, the rings were transferred into 16 x 125 mm glass tubes containing 1.0 ml fresh HEPES BME, placed on the roller drum, and observed daily for continued or return of ciliary activity.

RESULTS

Tables 1-4 show the results of microtiter well immersion testing of the various dilutions of the anesthetic drugs.

TABLE 2. EFFECT OF TETRACAINE ON CILIARY ACTIVITY

Tetracaine Solutions	*% Ciliary Activity by Duration of Exposure* 0 min	1 min	2 min	5 min
2.0%	94	0	0	0
1.0%	100	0	0	0
0.5%	94	52	0	0
0.2%	98	84	45	0
Control fluid	93	100	100	93

TABLE 3. EFFECT OF COCAINE ON CILIARY ACTIVITY

Cocaine Solutions	*% Ciliary Activity by Duration of Exposure* 0 min	2 min	5 min	10 min
10.0%	96	5	0	0
7.5%	96	67	5	0
5.0%	96	51	0	0
2.5%	95	66	7	0
Control fluid	100	100	100	100

Hexylcaine produced a complete cilia stopping effect (CSE) at five minutes for the 5% and 2% strengths, and in the 1% and 0.5% dilutions, the CSE was complete in 20 minutes (Table 1). Tetracaine 2% and 1% produced a complete CSE at one minute of immersion; tetracaine 0.5% and 0.2% caused a complete CSE at two and five minutes respectively (Table 2). Cocaine required ten minutes to produce a total CSE in all dilutions (Table 3). Lidocaine caused total CSE in 5 minutes for the 4% and 2% strengths, and the 1% and 0.4% solutions caused complete CSE in 10 and 20 minutes respectively (Table 4). The ciliary activity of the control cultures immersed in HEPES BME ranged from 93-100% throughout the study period. When the rings were removed from the wells and placed in fresh HEPES BME in roller tubes and observed the

TABLE 4. EFFECT OF LIDOCAINE ON CILIARY ACTIVITY

Lidocaine Solutions	*% Ciliary Activity by Duration of Exposure* 0 min	2 min	5 min	10 min	15 min	20 min
4.0%	95	39	0	0	0	0
2.0%	94	57	0	0	0	0
1.0%	95	65	40	0	0	0
0.4%	100	64	34	25	0	0
Control fluid	98	95	94	94	94	96

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[*] Microbiological Assoc., Bethesda, MD.

TABLE 5. CILIARY ACTIVITY IN CHICKEN EMBRYO TRACHEAL ORGAN CULTURES 24 HOURS AFTER REMOVAL FROM TEST DRUGS IN MICROTITER WELLS AND INCUBATION IN ROLLER TUBES

	% Solution	*% Ciliary Activity*
Hexylcaine	5	0
	2.5	0
	1	0
	0.5	0
Cocaine	10	0
	7.5	0
	5	0
	2.5	66
Lidocaine	5	0
	2	0
	1	90
	0.4	98
Tetracaine	2	0
	1	0
	0.5	0
	0.2	96
Control fluid		89

TABLE 6. CILIARY ACTIVITY IN CHICKEN EMBRYO TRACHEAL ORGAN CULTURES IN ROLLER TUBES AFTER TRANSTRACHEAL IN VIVO INJECTION OF ANESTHETIC AGENTS, HEPES BME, AND DISTILLED WATER

	% Ciliary Activity by Time Elapsed		
Agents Tested	*0*	*1 day*	*3 days*
Lidocaine 4%	95	95	52
Cocaine 5%	85	75	75
Hexylcaine 5%	90	0	0
Tetracaine 2%	92	0	0
Control fluids	97	95	75
Distilled water	90	51	23

following day for any return of ciliary function, only those rings exposed to the most dilute solutions had any recovery of ciliary function (Table 5). Ninety-six percent cilia function was seen following the 24-hour period of roller drum incubation in the 0.5% tetracaine treated cilia and 66% in the 2.5% cocaine treated rings. In those rings immersed in the two most dilute lidocaine dilutions, 90 and 98% ciliary activity was noted for the 1% and 0.5% treated rings respectively. No ciliary activity was present the following day in any of the hexylcaine treated rings.

The effects upon in vitro activity of cilia from tracheas injected in vivo are presented in Table 6. No ciliary activity was observed in those rings from tracheas injected with hexylcaine 5% and tetracaine 2%. On the third day after transtracheal injection of lidocaine 4%, cocaine 5%, control fluid, and distilled water, the ciliary activity was 52%, 75%, 75%, and 23% respectively.

DISCUSSION

The anesthetic agents were tested in two different ways. In the first, the tracheal rings were immersed in the test drugs, and ciliary activity observed until it ceased. This kind of testing showed that ciliary activity was stopped by all the drug dilutions in a time span that ranged from 1-20 minutes, even when the tracheal rings were immersed in dilute solutions of the anesthetic agents. When ciliary activity ceased and rings were returned to tubes containing fresh HEPES BME medium and incubated at 37 C on the roller drum, some ciliary activity had returned when observed 24 hours later but only in those rings exposed to the most dilute strengths of the test drugs.

When the anesthetic drugs were used in concentrations and by a method approximating their use in endoscopy, that is, by injection directly into the tracheas of embryos, two of the drugs produced marked ciliotoxicity. Hexylcaine and tetracaine treated tracheal rings when examined one and three days after the transtracheal injection showed no ciliary activity. In contrast to this, the ciliary activity in tracheas injected with lidocaine and cocaine did not differ significantly from the ciliary activity observed in tracheas injected with the control fluid.

Since cilia are identical wherever they are found on the phylogenetic scale[9] and the ultrastructure of chicken trachea cilia is identical to human cilia (Fig. 1), the organ culture system has

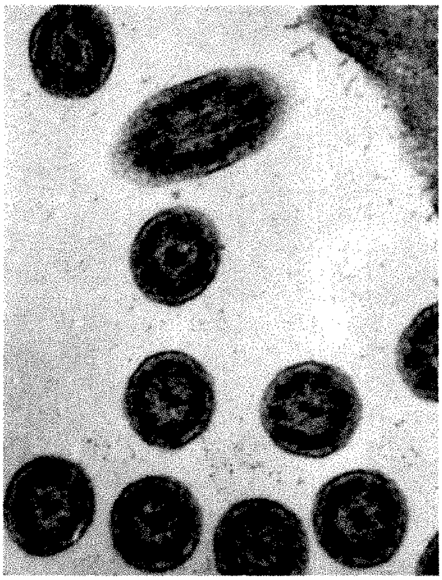

Fig. 1. Ultrastructure of cilia from a chicken embryo tracheal organ culture demonstrating the presence of the 9+2 microtubule pattern: nine pairs of microtubules around the limiting membrane of the cilia and two central microtubules. Dynein arms can be seen extending from the microtubules.

been suggested as a useful method to evaluate ciliary function.[10] The chicken embryo tracheal organ culture system is especially well-suited for this, for large quantities of organ cultures containing motile cilia are easily obtained by the method outlined. The rings which adhere to the side of the tube are cross sections of the trachea. Using an ordinary microscope, mass ciliary movement is easily observed. An added advantage which this method provides is the ability to clear debris from within the ring by shaking the screwtop tube. This permits the beating cilia to be viewed in a ring free from the presence of obstructing cellular detritus.

The reasons for the discrepancy in the findings between the two tests are difficult to discern. A low pH and the presence of preservatives are two reasons that could be offered to explain the marked ciliotoxicity of some of these agents, for tetracaine has a pH of 4.63 and the two most ciliotoxic anesthetic agents contain as preservatives methylparaben and propylparaben (hexylcaine) and chlorbutanol (tetracaine). Negus[11] reported that ciliary activity is diminished when the pH is less than 6.4. Although cocaine and tetracaine contain chlorbutanol as a preservative and although their toxicity for cilia is similar when they are tested by total immersion, their effect on ciliary activity is very different when tested by injection into intact tracheas. It would appear that the toxicity of tetracaine when injected in vivo may be related to its pH but probably is not related to the preservative it contains.

Although none of the agents was well-tolerated by cilia, using total immersion testing, the use of a method more nearly approaching that used in clinical practice produced surprising results. The instillation of tetracaine and hexylcaine directly into tracheas produced a total loss of ciliary activity, while a single injection of cocaine 5% or lidocaine 4% produced changes in ciliary activity little different from those seen in tracheas injected with control fluid. Although neither hexylcaine nor tetracaine is frequently used, endoscopists and other otolaryngologists should be aware of the ciliotoxicity produced by these agents.

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AMERICAN CLEFT PALATE ASSOCIATION

The program committee planning the next meeting of the American Cleft Palate Association to be held in San Diego, CA, February 25-March 1, 1979 is soliciting papers, exhibits, motion pictures, etc. The deadline for submission of abstracts is September 30, 1978. W. S. Garrett, Jr., MD, Program Chairman, 3600 Forbes Avenue, Pittsburgh, PA 15213.

* * *

VOICE RESEARCH

A project is currently underway at Southern Illinois University at Carbondale, Illinois, which has established a Computerized Register of Voice Research (CRVR). CRVR consists of a computerized bibliographic data base dealing with literature and research in the area of voice: singing voice and pathological voice. The data base includes citations of applicable literature dating to January 1975 taken from such sources as journal articles, books, research projects underway, published and unpublished dissertations, published and unpublished research, and book reviews. The purpose of CRVR is to eventually provide a research tool and communication link for researchers and educators internationally who are interested in voice. The system is designed so that any individual may request a listing of recent literature, research efforts, and/or research presently underway for whatever interest area or purpose.

It is possible to provide specific subject searches of the data base as requested by an investigator, for example, producing citations on such topics as respiratory training of singers and nonsingers or esophageal speech for the laryngectomized patient. If requested, we can provide a bibliographic display of all articles, research, and/or dissertations by a specific author or provide that author's current address.

More information may be obtained by writing to: Theophil M. Otto, Assistant Professor, or Mark J. Ashley, Research Assistant, Morris Library, Southern Illinois University at Carbondale, Carbondale, IL 62901.

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BIOMECHANICAL CHARACTERISTICS OF THE CANINE TRACHEA

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The trachea is a dynamic organ that responds to the demands of deglutition, respiration, and gravity. Following tracheal resection, reconstruction should allow the trachea to assume its dynamic functions. Experiments in dogs revealed that mercury-in-silastic strain gage apparatus can successfully be used to measure the biomechanical dynamics of the trachea and subglottis. The upper tracheal segments assume a larger stress load than the lower tracheal segments following tracheal resection.

The physiology of the trachea as a dynamic organ has been glaringly neglected in the medical literature. Although several authors have elucidated the function of the tracheal mucous membrane, cilia function, secretion production and mucus transport rate,[1,2] only scant reports deal with the biomechanical properties of the tracheal wall.[3-6]

Although arising from an embryonic derivative which ultimately forms the esophagus, the trachea and bronchial tree respond to unique demands which are distinct from the digestive apparatus. The few studies reported on tracheal physiology clearly show it to be a dynamic, complex organ, designed to cope with distinct physiologic demands. The trachea is not a static tube, merely connecting the larynx with the bronchus, but instead a structure which responds to the stresses of respiration, airway protection and deglutition.

The present study of the biomechanical properties of the tracheal wall was initiated to clarify some aspects of normal canine tracheal physiology in vivo, to test a mercury-in-silastic strain gage apparatus, and to document alterations which occur in the stress-strain characteristics of the tracheal wall following segmental tracheal resection.

METHODS AND MATERIALS

Strain (elongation) across the intercartilaginous membranes was measured utilizing Whitney mercury-in-silastic strain gages (Parkes Electronics Laboratory, Beaverton, Oregon). The gages were modified to 3 mm of active length and .38 mm diameter. During the insertion, the gages were stretched slightly, that is, preloaded, to assure linearity of response.

To determine the linearity of each gage prior to use, gage factors were calibrated utilizing a micrometer and voltmeter. Expressed as the ratio of the percentage resistance change to the percentage elongation $\left(\frac{\Delta R}{R_0} \Big/ \frac{\Delta L}{L_0}\right)$, the gage factor is an indication of the change in electrical resistance flowing through the system as the length of the gage changes (Fig. 1). Strain, therefore, can be expressed as a change in resistance through the strain gage.

To determine a standard "stress-strain" curve of the cricotracheal membrane, a section of cricoid, first tracheal ring, and the connecting intercartilaginous membrane were removed from a dog. The cross-sectional area of the membrane was determined, and a micrometer and force gage were used to measure the strain and stress (force per unit area) of the sample material.

Having calibrated the gages and having determined the stress characteristics of the cricotracheal membrane, several experiments were performed to examine the in vivo biomechanical characteristics of the tracheal membranes in a normal dog and following tracheal resection.

Adult pound dogs weighing 25 kg were used for all studies. Animals were anesthetized with .2% methohexital (Brevital®) drip via an in-

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Presented at the meeting of the American Broncho-Esophagological Association, Palm Beach, Florida, April 24-25, 1978.

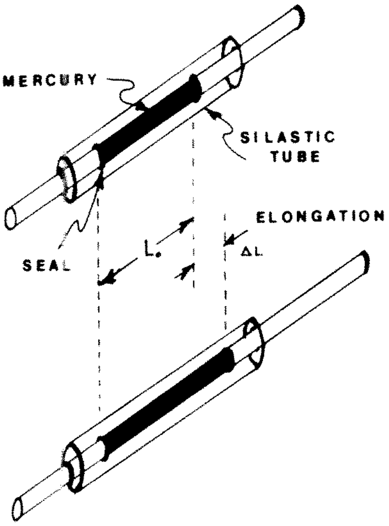

Fig. 1. Whitney strain gage.

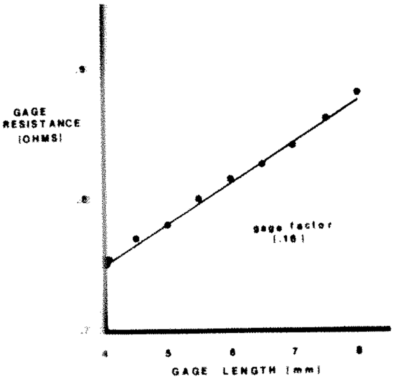

Fig. 3. Gage characteristics.

travenous catheter in the cephalic vein and oxygenated via an endotracheal tube. The plane of anesthesia was maintained following placement of the gages so that the swallowing reflex was intact.

Following anesthetization, in the supine position with the head extended on the neck, a vertical midline cervical incision was made and the thyroid cartilage, cricoid cartilage and trachea exposed from the hyoid bone to the suprasternal notch. Strain gages were secured to either the cricoid cartilage or the tracheal cartilages with 4-0 silk sutures.

Once secured, gages were used in a system depicted in Figure 2. A constant current generator of 100 mma for each channel of four channels was used to provide the change in resistance. A four channel recorder* was used with model 7P1 low level DC preamplifier. The amplifiers were calibrated in each channel and the offset voltage and gain were adjusted to give recordings on paper.

Mercury-in-silastic strain gages were placed across the cricotracheal membrane, and in series over the first, second, and third tracheal membranes. The effect of hyperextension of the neck and of deglutition was measured.

A strain gage was placed across the cricotracheal membrane. Utilizing a force gage, the larynx was elevated, the force of elevation measured, and the resulting $\frac{\Delta L}{L}$ noted. Following this measurement, the third to the sixth tracheal rings were resected and a primary

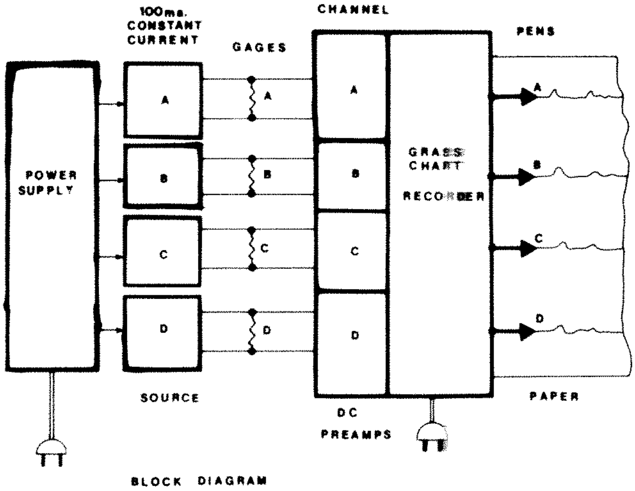

Fig. 2. Description of electrical apparatus used to measure tracheal tension.

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*Model 7. Grass Instrument Co., Quincy, MA.

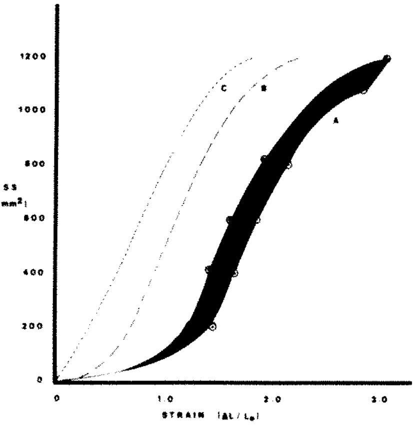

Fig. 4. Characteristics of canine tracheal intercartilaginous membrane.

anastomosis performed. The effect of tracheal resection was then determined by remeasuring the tension across the cricotracheal membrane.

RESULTS

Gage Calibration. Figure 3 represents the results of response of a typical mercury-in-silastic gage used. Gage factors

$$\frac{(\text{change in resistance/change in length})\ (\triangle L)}{(\text{original resistance/original length})\ \ (L)}$$

varied between .16 and .39. The gages demonstrated good linearity of response and were found to be a reliable, accurate method of measuring tracheal strain. The gages were easily secured to the tracheal cartilages, could be connected in series, and could be adapted to measure several physiologic phenomena. In addition, the gages are sterilizable, and following initial determination of gage factor, can be used repeatedly.

Material Test. The elastic modulus for the canine cricotracheal membrane is shown in Figure 4. Several samples were tested and showed similar patterns. With the initial change in strain, there was documented little change in stress across the membrane. With increasing elongation, however, the force/unit area increased rapidly and in a linear fashion.

Tracheal Dynamics During Head Extension and Swallowing. Table 1 shows $\frac{\triangle L}{L}$ for each gage placed. With hyperextension of the head and the neck, measurements indicate that the cricotracheal membrane lengthens to 64% of its original length. The lower rings appear to lengthen less rapidly; the third tracheal membrane lengthens the ring by only 4.8%. Similar recordings taken during swallowing indicated a similar pattern (Table 2).

TABLE 1. EFFECT OF HEAD EXTENSION

Gage	*Location*	$\frac{\triangle L}{L}$	*Gm/mm²*
A	Cricotracheal membrane	.64	625
B	1st-2nd tracheal ring	.37	375
C	2nd-3rd tracheal ring	.12	110
D	3rd-4th tracheal ring	.047	57

TABLE 2. EFFECT OF SWALLOWING

Gage	*Location*	$\frac{\triangle L}{L}$	*Gm/mm²*
A	Cricotracheal membrane	.62	600
B	1st-2nd tracheal ring	.33	325
C	2nd-3rd tracheal ring	.11	100
D	3rd-4th tracheal ring	.05	50

Effect of Tracheal Resection. Table 3 shows the effects of tracheal resection on $\frac{\triangle L}{L}$. Whereas the cricotracheal membrane stretched 40 and 60% with increasing upward force on the larynx, following tracheal resection it stretched only 30 and 36% respectively.

TABLE 3. EFFECT OF TRACHEAL RESECTION

Force	*Preresection* $\frac{\triangle L}{L}$	*Postresection* $\frac{\triangle L}{L}$
907 gm	.40	.30
1814 gm	.61	.36

DISCUSSION

The advent of the positive pressure breathing apparatus and endotracheal intubation has seen a concomitant rise in cases of subglottic and tracheal stenosis.[7] In past years, the treatment of laryngotracheal stenosis has consisted of dilatations with or without partial or complete removal of scar tissue and stenting. Recently, however, tracheal or subglottic resection with primary anastomosis has become the treatment of choice.[8,9]

Primary end-to-end tracheal anastomosis was first reported in 1885.[10] Since that time, several authors have contributed to refinements in technique.[11,12] These improvements aside, however, tracheal resection with end-to-end anastomosis still results in significant morbidity or restenosis.[13] Despite meticulous surgical technique, steroids, neck immobilization and tracheal mobilization in the neck or thorax, restenosis occurs with distressing frequency. The critical factor of tension across the tracheal suture line seems to determine the amount of tracheal wall which safely can be removed. Indeed, the tension needed to reapproximate the trachea following resection is exponentially related to the amount of trachea resected.[14]

The success or failure of primary anastomosis can be predicted on the basis of tension under which the anastomosis is performed. Maeda,[15,16] Ferguson et al[17] and others[14] have found that tensions greater than 1750 gm in adult dogs and 1000 gm in puppies, result in restenosis or wound disruption. A precise understanding of the biomechanics of the tracheal cartilaginous membrane seems essential, therefore, if methods of reducing tension across a tracheal suture line are to be developed.

The present investigation demonstrates that the canine trachea is a complex, dynamic organ. When subjected to varying stresses of gravity or position, tensions and forces are redistributed in a predictable fashion. This supports the findings of other investigators who noted that when moving from the supine to the head-up position, the canine tracheal bifurcation is lowered without tension on the lung buds, an event which could induce alveolar deformation and pathophysiologic effects.[18]

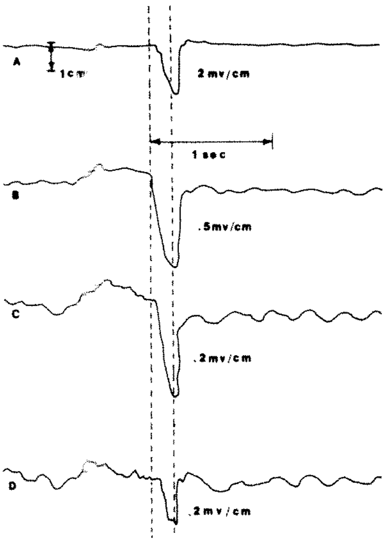

Fig. 5. Sequential strain recordings of four upper segments.

Since the normal trachea is subjected to a complex support system,[19] measuring tension across the tracheal suture line is most accurately performed in vivo where the contribution of supporting ligaments can be assessed. Separating the trachea from its surrounding elements will give a distorted impression of these stresses incurred by deglutition, changes in position, and respiration. The mercury-in-silastic gage employed gives reproducible results without distorting tracheal or paratracheal anatomy.

Results of experiments utilizing several gages in series also give some insights into the mechanism of tracheal elasticity (Fig. 5). During swallowing, the lower tracheal rings separate first, followed by consecutive rings above them. The intercartilaginous membrane stretches before the force is transmitted to the next higher tracheal ring. Since the intercartilaginous membranes vary in width, and since each higher membrane is subjected to increasing forces of gravity, following tracheal resection the upper rings tend to reach saturation rapidly and are subjected to stress and strain disproportionate to the lower rings.

Any successful reconstruction of the trachea following resection should be measured by the resultant anatomic, physiologic, and biochemical properties of the reconstructed segment. Although the primary objective is for the most part establishing an adequately sized tracheal lumen, secondary goals include reproducing the normal tracheal stress-strain relationships, reestablishment of the mucus production and flow characteristics of the tracheal mucous membrane, and normalization of tracheobronchial-pulmonary mechanics.

It seems likely that scar tissue between cartilage rings, bridging a tracheal anastomosis, is a poor biomechanical substitute for a normal intercartilaginous membrane. Substituting tracheal prostheses, however, has been unsuccessful. Although most surgical procedures advocated for rebuilding the trachea have centered on the size of the resultant lumen, additional attention should be directed toward the dynamic ancillary functions of the trachea.

Since tension across the tracheal suture line contributes to the extent of subsequent restenosis, the development of a measuring device, used in the operating room, which could indicate the maximum allowable limits of resection, would greatly contribute to the reduction of cases of restenosis. The mercury-in-silastic strain gage seems to be adaptable to measuring the limits of tracheal resection in humans. Indeed, these investigations indicate the extent to which the stress-strain curve is altered, that is, shifted to the left (Fig. 4[c]). Such changes in stress possibly contribute to subsequent restenosis.

The investigations performed during swallowing and after hyperextension of the neck show that the upper segments of the trachea are a more mobile and dynamically active part of the trachea than the lower segments. Most of the strain of tracheal elongation is assumed by these upper tracheal structures.

In addition, when the membranes are stretched and placed under additional resting stress, that is, they are preloaded, as following tracheal resection, then the elastic modulus shifts to the left. As a consequence, the anastomosis is subjected to additional tension with possible restenosis.

In summary, the limits of tracheal resection can be hypothesized, utilizing the described technique. Follow-up studies correlating the incidence of restenosis with tracheal suture line tensions in vivo will hopefully enable us to devise alternate means of tracheal reconstruction with less morbidity attending those procedures currently utilized.

CONCLUSIONS

1. The trachea is a complex, dynamic organ with distinct biomechanical characteristics.

2. Successful reconstruction of the trachea, in addition to preserving the size of the lumen, should also attempt to reestablish the normal stress-strain characteristics and mucous membrane functions.

3. The upper segments of the trachea are a more mobile and dynamically active part of the trachea than the lower segments.

4. Further investigations into the normal and pathologic tracheal membranes are necessary to devise alternative means of tracheal reconstruction and immobilization following tracheal resection.

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BIOLOGICAL EFFECTS OF NOISE

The International Commission on Biological Effects of Noise announces the Third International Congress on Noise as a Public Health Problem: Biological and Behavioral Effects, September 25-29, 1978 in Freiburg, Federal Republic of Germany (West Germany). Inquiries should be addressed to: International Commission on Biological Effects of Noise, Institut für Arbeits- und Sozialmedizin, Universitätsklinikum, Johannes Gutenberg Universität, Obere Zahlbacher Strasse 67, D-6500 Mainz, Federal Republic of Germany.

Ann Otol 87:1978

MEDIASTINOSCOPY: THE PREDICTIVE SURVIVAL VALUE IN STAGING CARCINOMA OF THE LUNG

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One hundred and thirty-seven cases of Stage III lung cancer established by mediastinoscopy have been followed to determine their survival. The tissue was classified according to World Health Organization schema and the degree of dedifferentiation graded from well to poorly differentiated. Two percent of the presented cases are well-differentiated tumors; the remaining 98% are moderately well-differentiated (11%), or poorly differentiated or small cell tumors (87%). The degree of anaplasia suggests an increasingly aggressive metastatic behavior pattern. The average life span is approximately 5½ months in all groups and subgroups which were studied. Recommendations are presented for the utilization of mediastinoscopy in Stage I and II cases. Further considerations are suggested for priority of diagnostic procedures in establishing the diagnosis of lung cancer.

Cancer of the lung is such a grave disease that considerable study has been directed toward identification of the parameters which will predict patient survival. The extent of mediastinal metastases provides some guidelines for management of patients.

The authors' experience of 137 cases is presented with a retrospective analysis of survival with respect to cell origin, degree of dedifferentiation, and the location of lymphatic tumor spread. A prospective corollary of prognosis may be drawn from these data by comparing the tumor stage and cell type with the derived graphs of survival. Until such time arrives when progress in the modalities of care improves the cure rate or effects greater tumor suppression, we can assume these data to be relevant to the individual patient's course.

Surgery may have reached the zenith for resectability and curability; more effective screening techniques for early diagnosis and development of highly selective chemotherapeutic agents probably represent the ultimate tools of success.

There are some considerations and statistics about cancer of the lung that need be reviewed as background material before presentation of the authors' data. From a historic viewpoint, Harting and Hesse[1] in 1897 recognized the malignant nature of this disease which they erroneously labeled pulmonary sarcoma. The accurate diagnosis was established in 1913, and a review of the world literature by Adler[2] at that time collected no more than 374 cases. The spectacular progression of cancer of the lung is a phenomenon of the 20th century.

Incidence. The most significant fact is that the total number of lung cancers developing each year is increasing with the sharpest rise of all malignant neoplasms. In the period from 1930 to 1974, the age adjusted cancer death rates for selected sites in males in the United States emphasized an increased incidence from 4 to 52/100,000 or 13-fold. The estimated new cases for 1977 are 98,000, of which 76,000 are male and 22,000 female. From the 1976 data, in Caucasian males, cancer of the bronchus and lung occurred with an incidence of 89.9 per 100,000.[3] The trend in cancer of the lung in females indicates an increase almost as great as that in males. Further, 22% of all malignancies

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Presented at the meeting of the American Broncho-Esophagological Association, Palm Beach, Florida, April 24-25, 1978.

in the male have the site of origin in the lung corresponding to 6% in females, second to breast cancer at 26%.[4]

Cure Rate. The cure rate has improved somewhat from the early 1950s to the late 1960s, though it is still at a discouragingly low figure. When the patients with localized disease are considered, improvement in the 5-year survival measured from 21% to 33%. Regional disease prognosis improved as well, though not at the same magnitude as those with the localized form of disease. The prognosis of patients with distant metastases was poor overall and improvement was evident only in one year survival rate.[3]

Success of cure relates to early diagnosis and the degree of extension of the disease at the time of identification. From the same data,[3] we note that 40% of the cancer of the lung and bronchus are localized or regional. Five-year survival of all stages is 9% and 33% for the localized stage in Caucasian patients. Corresponding data for Negro patients is 6% for all stages and 21% for localized disease. The current state of our knowledge concerning cancer of the lung suggests that the only hope for cure is surgical extirpation of the tumor.

Cell Type and Degree of Dedifferentiation. It is important to recognize that while lung cancer is considered as a single entity, it consists of four major histologic patterns with disparate behavior characteristics, specific cells of origin, individual tendencies toward localization or dissemination, and potential for curability. Epidemiological studies in the United States indicate that epidermoid carcinoma constitutes approximately 50% of all cancer, adenocarcinoma about 20%, undifferentiated small cell carcinoma about 20%, and undifferentiated large cell carcinoma the remaining 10%.[5] When considering prognosis, the factor of cell type, behavior, and doubling time must be added to the patient's general physical condition, cardiopulmonary function, age and ambulatory status.[6]

Location. The location of origin of the carcinoma is important with respect to staging, i.e., evidence of the lesion within 2 cm of the carina. Hinshaw and Garland[7] reported that 11% of the carcinomas arose in the main bronchus, including intermediate bronchus, 29% in the lobar bronchus, 29% in the segmental bronchus, and 31% in the segmental area, (i.e., peripheral lesion, usually arising from a subsegmental bronchus). Extension of the tumor either within the bronchial lumen or submucosal infiltration rapidly changes the gravity of the stage as the lesion involves the main bronchus and/or carina.

Staging. Staging[8] is based upon three factors: 1) the extent of the primary lesion, 2) nodal involvement, and 3) the presence of distant metastasis. The following conditions are classified as Stage III: T_3 with any N or M, N_2 with any T or M, M_1 with any T or N. The definitions of the TNM levels are as follows: T_3, a tumor of any size with direct extension into an adjacent structure such as the parietal pleura or chest wall, the diaphragm, or the mediastinum and its contents, or a tumor demonstrated bronchoscopically to involve a main bronchus less than 2 cm distal to the carina, or any tumor associated with atelectasis or obstructive pneumonitis of an entire lung or pleural effusion; N_2, metastases to lymph nodes in the mediastinum; M_1, distant metastases present. In summary, Stage III is any tumor more extensive than T_2, or any tumor with metastases to the lymph nodes in the mediastinum, or any tumor with distant metastases.

In addition to the TNM classification, the tumor cell types are grouped between Grade (G.)I, well-differentiated, G.II, moderately well-differentiated, G.III and G.IV, poorly to very poorly differentiated. This staging is applicable to survival of the cell types including squamous cell, adenocarcinoma and undifferentiated large cell carcinoma but it is not significant for the small cell carcinoma.

For this presentation, Stage III is based upon the fact that N_2 is established by mediastinoscopy and biopsy. In all instances, the tumor is present in the paratracheal region; we have ex-

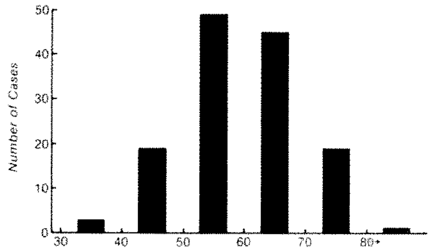

Fig. 1. One hundred and thirty-seven cases of lung cancer are evaluated by decade of life at the time of the initial diagnosis.

cluded the cases in which the metastasis is limited to the hilum. In addition, the patients are free of evident distant metastases, and the bronchoscopic examination excludes tumor within 2 cm of the carina.

RESULTS

We have reviewed our cases (137 total), and based the histologic interpretations upon the World Health Organization 1967 publication by Kreyberg.[9] One hundred twenty-six cases were followed to a terminal course. Of these cases, all but one died of cancer of the lung; the long-term sole survivor succumbed 5½ years later of secondary infection, (*Pneumocystis carinii*), while continuing immunosuppressant therapy. There are 11 survivors at the time of this compilation: one survivor six months, six survivors 6 to 12 months, two survivors 12 to 24 months, and two patients beyond 24 months. The surviving members of the study are entered into a program of chemotherapy and/or irradiation. Spectacular regression or disappearance of the mediastinal masses has occurred in many of these patients. Subsequent review of data will undoubtedly convert a number of temporary "improvement" or "cures" into the determinant fatal group. Mention is made of this currently surviving group to indicate that at this time, some patients fare reasonably well despite extensive disease at the time of the initial examination.

Age: Time of Diagnosis. It is well-recognized that lung cancer occurs with the greatest incidence in the diseased lung as the substrate, that is, in chronic bronchitis and previous pulmonary tuberculosis, and as the aging process diminishes the functional reserves. Our data of 137 cases is plotted by decades of life and parallels the established facts of increasing incidence with ascending seniority (Fig. 1).

Histology. The first consideration we entertained was whether there is a specific cell type of tumor which metastasizes with greater propensity to the mediastinal lymph nodes than other forms of lung cancer. Considered differently, was there a deviation toward greater incidence of metastases as the cell structure underwent a greater degree of dedifferentiation toward the anaplastic cell line? Reviewing the recent literature, the data taken from Armstrong and Bragg,[10] Silverman[3] and

TABLE 1. HISTOLOGIC TYPES OF LUNG CANCER

Histology	*Armstrong & Bragg*[10]	*Silverman*[3]	*Israel & Chahinian*[6]	*Welsh*
Epidermoid	35-60%	39%	30%	47%
Small cell anaplastic carcinoma	35%	7%	24%	28%
Adenocarcinoma	15-20%	Not specified 13%; alveolar cell 2%; mucin producing 1%	26%	18%
Large cell anaplastic carcinoma	5-15%		19%	3%
Bronchial adenoma	5-10%			Adenosquamous 1%
Cancer — not specified & unclassified		Cancer — not specified 34%; Misc 4%		Unclassified 3%

The low percentage of small cell anaplastic carcinoma is explained by the large group of cancer, not otherwise specified (34%) which contain a number of this group.[3]

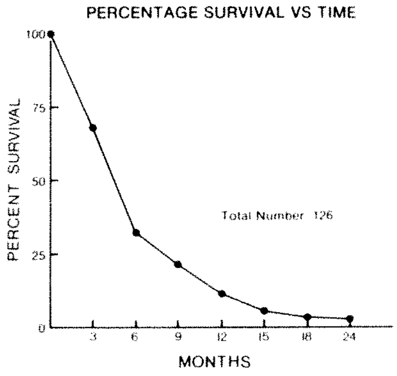

Fig. 2. Survival of 126 terminal cases is plotted from the time of diagnosis. The average life span is approximately 5½ months.

Israel and Chahinian[6] were used as references and comparison made to the authors' data (Table 1).

The epidermoid carcinoma form of lung cancer occurs between a low of 30%[3] and the high of 60%,[10] with the authors' data in range at 47%. Analysis of small cell anaplastic and adenocarcinoma indicates again similarity of data between the reference material and the material in this study. Discrepancy appears in the large cell anaplastic tumor when the authors' data are relatively low with 3% of the total. The authors recognize that individual interpretation among pathologists is sufficient to explain several percentage differences in the anaplastic tumor forms. The epidermoid and adenocarcinomas can be distinguished according to the degree of anaplasia and the cases distributed into the categories of well-differentiated, moderately, and poorly differentiated type.

Survival. We shall consider the 126 determinant terminal cases and plot the survival time in months following confirmation of tumor by mediastinoscopy and biopsy. A precipitous fall of survival can be observed to the sixth month. Thereafter, the 25% surviving group drops more slowly to 3% at 18 months or more (Fig. 2).

Next we investigated the length of survival versus the histologic type and degree of dedifferentiation (Table 2). We observe that the well-differentiated tumor, whether epidermoid or adenocarcinoma, is uncommon in these data; occurring in 1 of 62 of the former and again 1 in 22 of the glandular tumors. The large cell anaplastic and unclassified tumors have been discarded from survival analysis due to the low percentage of these data (6% total) (Fig. 3).

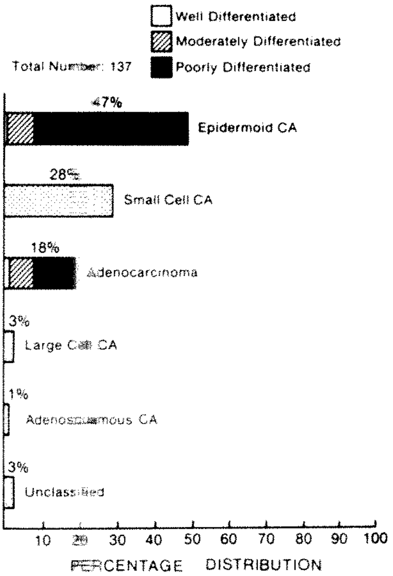

Fig. 3. Breakdown of the 137 cases by tissue type and degree of differentiation.

TABLE 2. SURVIVAL VS CELL DIFFERENTIATION

	Epidermoid		*Carcinoma Adeno*		*Small Cell*	
	No.	*Mo*	*No.*	*Mo*	*No.*	*Mo*
Well-differentiated	1		1			
Moderately well-differentiated	11	4.9	6	4.8	37	5.9
Poorly differentiated	50	5.7	15	8.6		
Overall average		5.7		5.3		

DISCUSSION

The authors are aware that the average survival of 5½ months in these cases (126) is extremely brief and that other surgical survival data[11] indicate a much greater cure rate and long-term success. The presented cases are in fact far advanced even though by definition they can be classified as Stage III. The presentation as superior vena caval obstruction, marked tracheal deviation due to extrinsic pressure, periesophageal metastases with resulting dysphagia, multiple neurological disorders (recurrent laryngeal and phrenic nerve), and direct extension into the adjacent osseous structure indicate the far advanced course of the disease. Certainly, not all of the cases presented with one or more of the above findings, but radiologically, in almost all instances, tomography indicated widening of the mediastinum with or without nodular masses.

In light of the above data, let us consider the cases which have been selected for diagnostic mediastinoscopy. As the concept of staging of lung cancer becomes universally applied, proper identification of the location of the lesion by appropriate diagnostic radiology is mandatory and should be sequentially followed by bronchoscopy to define the location within the tracheobronchial tree. The problem of mediastinal metastases is evaluated by tomography and mediastinoscopy. The presence of symptomatic distant metastases is indicated by appropriate roentgenograms, radioactive scans and, if need be, bone or soft tissue biopsy. Mediastinoscopy and biopsy are essential not only in the staging procedure but for providing tissue for other neoplasms of the mediastinum which would be treated by a nonsurgical approach, such as Hodgkin's disease, non-Hodgkin's lymphoma, sarcoidosis and others.

In our experience, positive tomography of the mediastinum rarely fails to yield diagnostic tissue while negative tomograms often suggest a failure to provide positive tissue at mediastinoscopy. Nonetheless, a negative tomographic study is not a contraindication to surgery particularly if there are other supportive evidences of metastases, such as hoarseness due to recurrent nerve paralysis or esophageal compression.

We do not recommend the interspace mediastinotomy for the presence of mediastinal metastases as the preferred technique of evaluation. It is true that if the surgeon identifies tumor through this relatively small exposure, it is a positive yield. The procedure is limited by space to a rather restricted field and a far greater area of concern with metastatic tumor can be presented though undetected in that examination.

The gross findings at mediastinoscopy may vary considerably. In general, we have found that metastatic tumor may be well-localized within a lymph node or the lymph node site may be grossly normal with small deposits of tumor cells microscopically evident throughout a number of nodes. A more extensive state of the disease indicates breakthrough of the capsule by the tumor into the adjacent connective tissue with little discernible nodal structures. Finally, a state of "fixed or frozen" mediastinum develops. Mediastinoscopy can be carried out but with an increased surgical risk due to bleeding. Fixation clearly indicates perivascular compression if not actual intravascular invasion of tumor. In this situation, punch biopsies of the connective tissue yield sheets of tumor cells generally without an overall structural pattern, i.e., keratin formation or glandular arrangements.

A number of cases (18) presented with hoarseness due to left recurrent nerve paralysis. These patients denied pulmonary symptoms though the chest x-rays were abnormal. Two of these cases were peripheral lesions, had negative tomography, and negative examination at mediastinoscopy. At thoracotomy, the site of the recurrent nerve invasion was on the anterior aspect of the aorta beyond the range of endoscopic dissection. Approximately six cases had right recurrent laryngeal nerve paralysis, in each instance, the diagnosis could be established by mediastinoscopy.

Superior vena caval obstruction due to tumor extension with venous distension and facial edema is a relative contraindication to mediastinoscopy. If the tissue diagnosis cannot be established by bronchoscopy, minor degrees of caval obstruction do not preclude surgical exposure of the mediastinum. The location of the obstruction is uniform and direct exposure into this area can be achieved with a high yield of tissue containing tumor. Reviewing our cases of this type, we noted a large volume of tumor mass, often without lymph node pattern, surrounding and fixing the right paratracheal region. When severe venous obstruction could be partially alleviated by radiotherapy, then biopsy was successful without excessive bleeding in all instances.

Direct chest wall extension or thoracic spine metastases suggest a very grave prognosis. Esophageal obstruction particularly in the upper or mid-third indicates either direct extension or periesophageal metastases. In our series of esophageal compression (six cases), the tumor extension was massive and sufficient tissue was available for biopsy. The pulmonary apex lesion or superior sulcus syndrome with arm, neck, and shoulder pain has been difficult to appraise by endoscopy. Neither bronchoscopy nor mediastinoscopy has been fruitful in this situation; it appears that the lesion is too peripheral for the intraluminal examination and metastases have not been located unless the tomograms have been positive.

While the presented data are taken from Stage III cases, it is worthwhile to evaluate the relative frequency of mediastinal metastases in those cases which could be considered as Stage I or II on the basis of the radiological appearance. The Stage I cases are those which appear as a small peripheral lesion, i.e., a nodule without evidence of disease elsewhere. We have reviewed 39 cases falling into this category which have undergone mediastinoscopy and find that only 3 (8%) have positive mediastinal nodes. We have therefore discontinued this procedure for this stage since 92% have been retrospectively unnecessary. Further, the patients have been subjected to a surgical procedure and consequent risk with minimal expectation and yield. The Stage II cases are those which are more extensive but without mediastinal widening or nodularity. In this group, we continue to recommend mediastinoscopy since the yield, while less than 50%, is significant. Our current data reflect a positive result of 25 to 30% and appear worth the surgical risk.

Stage III cases require an individual evaluation as the other stages, and in general, it would appear that the priority for examination would be directed to the tumor site making the lesion least feasibly treated by thoracotomy. For example, cutaneous or soft tissue nodules and some osseous metastases lend themselves to tissue biopsy with less risk than other approaches. In addition, the bone biopsy for osseous metastases would preclude further surgery. The "stroke" patient who in fact has cerebral metastases from lung cancer is studied with less risk by endoscopy than craniotomy. Palpable supraclavicular or cervical malignant adenopathy should be studied by needle or excisional biopsy before more hazardous endoscopic procedures or thoracotomy are entertained.

The last area of consideration is the high percentage of cases in this study which are either poorly differentiated or small cell carcinomas. These cell types reflect the highly malignant behavior pattern of these aggressive neoplasms. By contrast with the isolated well-differentiated epidermoid carcinoma with a reasonably encouraging prognosis after resection, these tumors have already presented as an inoperable state.

Our final comment is in support of staging by the available techniques outlined in this paper. With the gradual advance of new systems of care, the thoracotomy for cure should be the standard of care; thoracotomy for tissue diagnosis but not curative resection should be the last approach only when the other diagnostic techniques have failed.

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Ann Otol 87:1978

INSUFFLATION ESOPHAGOSCOPY

E. TH. EDENS, MD

GRONINGEN, THE NETHERLANDS

A new electroscope has been designed from the conventional Haslinger tubes. The new rigid scope combines the advantage of air insufflation in the flexible system with the therapeutic possibilities of the rigid tubes and is trustworthy in the following esophageal procedures: a) finding entrance of severe strictures; b) introducing nasogastric feeding tubes; c) extraction of foreign bodies; d) tumor coagulation/spur in hypopharyngeal diverticuli; e) washing and suction in cases with severe food retention; f) making tumor smears in patients with clotting disorders; g) taking substantial biopsies with an optical forceps, and h) objective photodocumentation of esophageal pathology.

It is more than 100 years ago that Kussmaul, an internist in Freiburg, Germany, entered the esophagus. From that time on there was a steady development in diagnostic and therapeutic possibilities.

The first concern of the designers was the need for more light. In the beginning there was a great difference between the European and the American school of endoscopy. In the old world nearly every endoscopist used the Haslinger esophagoscope with proximal light, while Chevalier Jackson from Philadelphia introduced the distal illumination. Mosher[1] mentioned the possibility of air insufflation for the treatment of webs of the esophagus.

Storz and Wolf recommended the use of their pneumatic optical esophagoscopes, but these scopes were relatively expensive for the general Ear, Nose and Throat specialists and used by only a few well-known esophagologists, such as Holinger and Brubaker,[2] and Savary and Miller.[3]

Nothing was heard about the use of air in the esophagus until the introduction of the flexible endoscopic systems. Working with the flexible scope, we enjoyed the view and new dimensions were discovered in the esophagus.

One of the disadvantages of the flexible system was the lack of therapeutic possibilities. The gastroenterologists in general have a great interest in the diagnostic procedures and leave the therapeutic cases to the ENT department. We therefore felt a need for a convenient rigid pneumatic scope to use in adults as well as in children, and transformed the conventional Haslinger esophagoscope into an all-duty insufflation endoscope. We designed a new electroscope made by Wolf, Knittlingen, W. Germany.

The mechanical part of the proximal end consists of a hollow tube with grip and inlets for the prismatic illuminator and twin bellows (Figs. 1 & 2). The whole system is sealed off by a Lehnhardt's universal cap in order to get the advantages of a phototelescope and biopsy forceps combined. Because of the danger of perforation, we abandoned the extension tubes in the original design of Haslinger and asked the instrument industry to manufacture extra tubes with 5 cm differences in length

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From the Department of Endoscopy E.N.T. Clinic, University Hospital, Groningen, The Netherlands.

Presented at the meeting of the American Broncho-Esophagological Association, Palm Beach Florida, April 24-25, 1978.

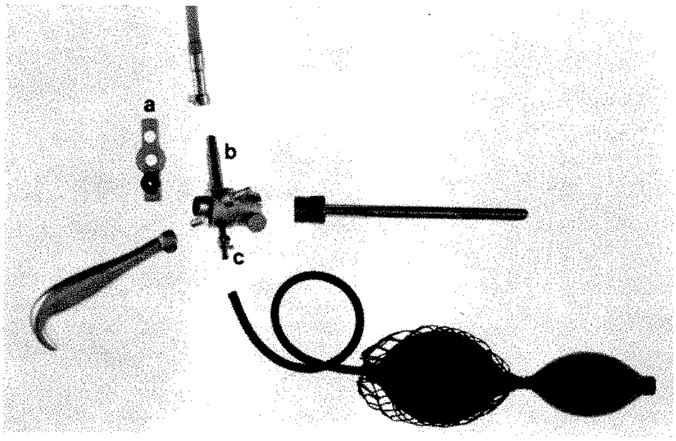

Fig. 1. a - Lehnhardt's universal cap; b - Prismatic illuminator; c - Air-inlet.

(from 25-50 cm). The endoscopist can choose the desired length according to the information on the x-ray pictures.

During the past two years we had the opportunity to test this new scope on 861 patients. It appears to be a great improvement in therapeutic endoscopy. Distention of the esophagus gives more information about the rigidity of the wall in patients with suspected malignancy. Excision, with the help of an optical biopsy forceps, gives four to six times the amount of tissue compared to the results with the small forceps used in flexible scopes. Careful inspection of a "difficult" foreign body is one of the conditions for a safe and smooth extraction. In patients with an extended hypopharyngeal diverticulum it is sometimes very difficult to find the esophageal lumen. Locating the esophageal inlet and properly adjusting the tissue bridge requires a lot of experience.[4] Air insufflation is the only way to open the lumen and to introduce a thin uretic catheter (Fig. 3). Objective photodocumentation is possible with the help of existing Storz and Wolf telescopes used in bronchoscopy. These telescopes are 45-47 cm length and are extremely satisfactory in routine procedures. They are unable to reach the cardia and so for this purpose an ACMI Katz esophageal telescope is used with a working length of 53 cm.[2]

Air insufflation is a great help in finding the entrance of a severe stricture and facilitates also the introduction of a nasogastric feeding tube in patients with progressive malignant stenosis.

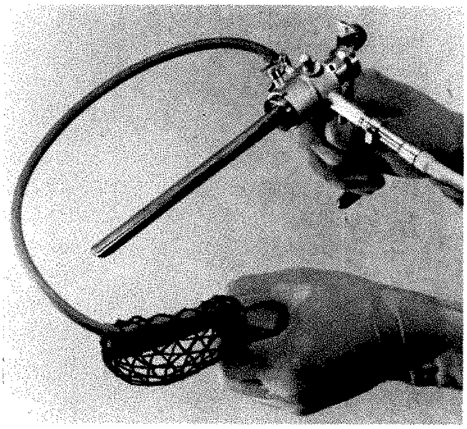

Fig. 2. Edens/Prins esophagoscope.

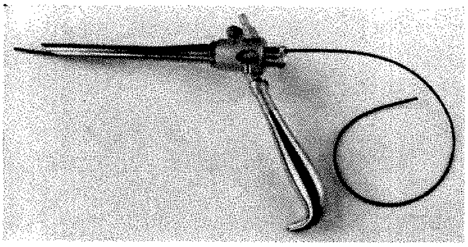

Fig. 3. Thin catheter locating the esophageal lumen in patients with hypopharyngeal diverticula.

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Acknowledgment — The technical assistance of Mr. C. T. Prins, chief technician, E.N.T. department, is greatly appreciated.

Reprints — E. Th. Edens, MD, Department of Endoscopy E.N.T. Clinic, University Hospital, Groningen, The Netherlands.

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XII WORLD CONGRESS OF OTORHINOLARYNGOLOGY

The XII World Congress of Otorhinolaryngology will be held June 21-26, 1981 in Budapest, Hungary. Preliminary communications, recommendations and suggestions, should be directed to Prof. Dr. L. Surján, President, XII World Congress of ORL, H-1389 Budapest, Pf. 112 Hungary.

Ann Otol 87:1978

NEW ENDOTRACHEAL TUBE FOR LASER SURGERY OF THE LARYNX

MARTIN L. NORTON, MD

PAUL DE VOS

NEWTON CENTER, MASSACHUSETTS

The risk of combustion of endotracheal tubes during laser surgery of the larynx has been demonstrated. A new flexible metal endotracheal tube has been developed to obviate this risk. The laser beam is dispersed by the construction of the metal tube, thus assuring protection from both combustion and reflection.

The use of the CO_2 laser for surgery has been accompanied by concern for the safety of the patient. This has been thoroughly studied in applications of this modality to Otolaryngology.[1]

In previous reports we discussed the techniques and problems involved in CO_2 laser microsurgery of the larynx.[2-4] Particular concern about fire hazards[5] led our efforts to develop a safe endotracheal tube for these procedures. We focused on the problem of combustion of the endotracheal tube (Fig. 1), a complication aggravated (with the CO_2 laser beam) by the high oxygen content of the anesthetic mixture.

We previously used a red rubber tube wrapped with aluminum tape to disperse the light beam (Fig. 2), thus preventing laser impaction and possible combustion of the endotracheal tube. Of further concern was possible tissue damage due to straying of the infrared CO_2 laser irradiation from the reflective surface of the foil-covered endotracheal tube. As long as no contact of the incident infrared beam onto the rubber tube is ensured, the margin of safety before combustion is more than adequate. Due to the high reflectivity of the aluminum foil little or no heating of the tube occurs. Because of the relative smoothness of the foil to the incident infrared beam, rays of high power-density (w/cm^2) can cause "hot spots" in the affected beam of sufficient energy to cause tissue damage. Such areas where an only partially defocused beam impacts may go unnoticed due to an obscured view (as on the anterior tracheal wall) or because the gradual heating of the tissue may produce no visible lesions.

While tubes wrapped with aluminum foil were generally suitable, we were not satisfied since variables existed such as the human equation in wrapping carefully and the manufacturing quality control factor relative to the tape and its adhesive backing. Occasionally the tape would become loosened and its edge cut into the tissues of the larynx. Studies, extending over a period of three years utilizing Teflon® (Dupont), flexible glass (Corning), ceramic, wire wound, and other materials demonstrated their unsatisfactory qualities.

We now report the development of a suitable endotracheal tube (V. Mueller Co., Chicago, IL, Norton tube) meeting all the characteristics required. The criteria we selected are as follows: 1) absolute noncombustibility during 100% oxygen flow-through, 2) deflection of the light beam in such a manner as to disperse the incident light rays (resultant rays must be divergent and not refocus the beam), 3) ease of sterilization, 4) long-term economy, 5) flexibility, 6) relative air tightness, 7) minimal reflection or glare interference with vision, and 8) atraumatic to tissue.

Figure 3 is a photograph of our endotracheal tubes. The instrument is

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Presented at the meeting of the American Broncho-Esophagological Association, Palm Beach, Florida, April 24-25, 1978.

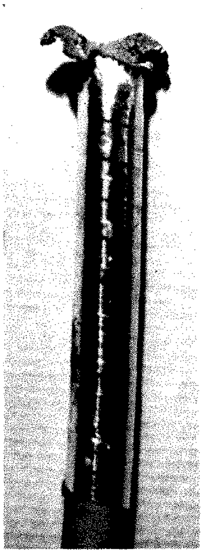

Fig. 1. Red rubber tube with burned tip.

made from stripwound hose using stainless steel or, as an alternative, wire wound square spring. This instrument is wire brushed or matte finished to diminish light reflection into the surgeon's field of vision. The use of the metal tube has the obvious advantage over the present delivery system in that it is a totally noncombustible, reusable item. This tube is relatively smooth and nonabrasive to the delicate laryngeal tissues. The reflectivity of this type tube to CO_2 laser radiation was investigated, in comparison with the foil wrapped tubes.

We used a He-Ne laser to model the pattern of reflection in a comparative study of foil-wrapped and flexible-metal endotracheal tubes. Because the He-Ne laser emits light in the red part of the visible spectrum, the direction and relative intensities of the scattered beam could be readily visualized. The beam was aligned tangentially to the tube and the scattered beam was projected onto a smooth flat surface, giving a cross-sectional plane through the maximal extent of the scattered light. Smoke was blown across the field to enhance the visualization of the reflected light rays. Photographs of these patterns in both tubes indicate an area of diffuse scattering of essentially equal intensity extending less than 1 cm radially from the impact site. Scattering from the aluminum foil wrapped tubes showed the integrity of the collimated incident beam partially maintained. Two rays of relatively high intensity were manifest in the reflected beam. By comparison, reflections from the flexible metal tubes indicated a generally more pronounced defocusing effect as evidenced by multiple fine rays of relatively low intensity.

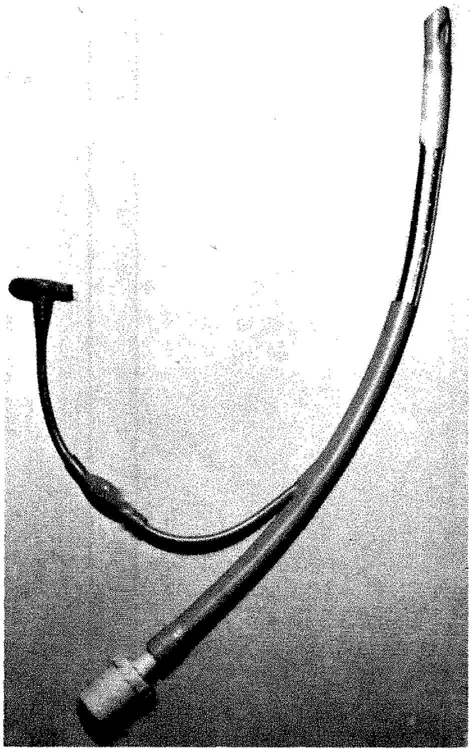

Fig. 2. Red rubber tube with aluminum tape to disperse the incident light bean.

Applying these observations to CO_2 laser scattering, it is expected that both tubes produce an area of low level but potentially hazardous heating immediately surrounding the impact site. With the foil-wrapped tube "hot spots" of high power-density (w/cm^2) can be expected. In our models, scattered radiation from the metal tubes is more equally distributed and therefore can be expected to be of lower power-density. Although this defocused radi-

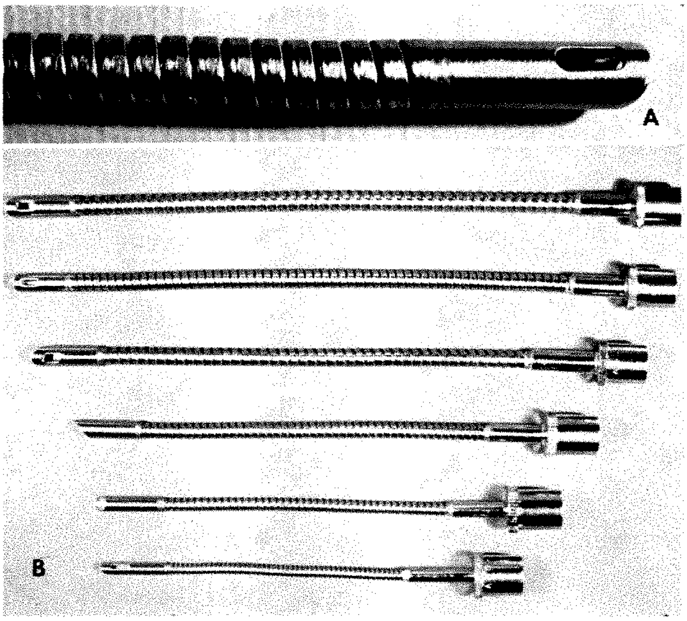

Fig. 3. A) Enlargement of tip of metal endotracheal tube. B) Endotracheal tubes of varying sizes (214 mm i.d. to and including 6.4 mm i.d.).

ation can be expected to have low vaporizing potential, precaution is indicated to protect against slow heating or blanching of the surrounding tissues.

These metal tubes are reflective at 10.6 μm (wave length of CO_2 laser used) and highly beam diverging. The reflected beam is more uniformly defocused than by the foil wrapped tubes, and "hot spots" are less intense. Absorption and subsequent heating of the tube occurred but was counteracted by the velocity of gas flow within the tube. Our studies included the various types of endotracheal tubes now available and the stainless steel flex-tube described herein. Dispersion of the light beam off the surface of the metal tube showed multiple fine lines of reduced power density. In contrast, the reflected beam from foil wrapped tubes showed fewer lines which are of high intensity and therefore of increased power-density with significantly higher potential for tissue damage from this "scatter radiation."

Generally, tissue damage from infrared radiation is a function of the absorption of the energy within the cell. This produces a boiling of the intracellular water followed by a rupture of the cell membrane and a vaporization of the cell content. Some residual carbonaceous material, probably representing the denatured protein of the cell, may be scattered. Thus, the effects of the laser are primarily related to the impact tissue, its constituency, and its absorption of the infrared irradiation. Varying the energy dosage of that radiation increased the number of cells affected rather than the manner in which its effects are produced. We recommend that when laser reflections from metal surfaces such as the endotracheal tube presents a potential threat, over-exposure of total delivered energy (joules/cm^2) be limited by minimizing the time component of the irradiation (by means of a time controlled shutter).

These endotracheal tubes have been used clinically for more than 77 patients (including both pediatric and adults). The problems demonstrated include: 1) Reflection of microscope light off the metal surface producing interference with vision. This was effectively mitigated by further matte finishing or rough buffing of the outer surfaces of the tubes. 2) The relatively rough segmentation of the endotracheal tubes may require special care in insertion of the direct laryngoscope to prevent the tip of the laryngoscope from catching on the segmental portion. While this can be somewhat annoying, it has not been a major problem.

The question of tissue receptivity of the metal endotracheal tube has been considered. We have seen no evidence of tissue trauma secondary to mechanical irritation from this device. Additionally, stainless steel is known to have excellent qualities of nonreactivity when implanted (eg, stainless steel sutures, femoral rods, pins, screws, etc). Even this potential problem is mooted when we recognize the extremely brief time the endotracheal tube resides within the larynx during procedures involving laser microsurgery of the larynx.

In summary, we have presented herein the solution to the last major problem involved in the use of the CO_2 laser for microsurgery of the larynx. The metal flex-tube described obviates any concern regarding flammability of endotracheal tubes during such surgery.

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REPRINTS — Martin L. Norton, MD, 48 Clark Street, Newton Center, MA 02159.

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ASSOCIATION OF OTOLARYNGOLOGISTS OF INDIA

The Association of Otolaryngologists of India will be holding its 31st Annual Conference at Nagpur January 11-14, 1979. For further information please contact: Dr. P. P. Karnik, Hon. Secretary, K.E.M. Hospital & G.S. Medical College, Bombay, India 400012.

Ann Otol 87:1978

FLEXIBLE FIBEROPTIC PEDIATRIC BRONCHOSCOPE

A NEW INSTRUMENT

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A new instrument, the pediatric flexible fiberoptic bronchoscope, is described. It is meant to be an adjunct to the routine open tube fiberoptic lit bronchoscopes and Hopkins rod system telescopes.

With the introduction of the flexible fiberoptic bronchoscope in 1970, new frontiers were opened. The diagnosis and treatment of pulmonary disease in the adult became more exact. The new bronchoscopes permitted a degree in instrumentation and examination of both the subsegmental bronchi and the upper lobes not previously possible.

Unfortunately this new class of flexible fiberoptic instruments was too large in diameter for the pediatric airway. Their average diameter was approximately 6 mm. A pediatric bronchoscope was available in the early 1970s which had a distal tip that was 3.2 mm in diameter. However, the diameter of the remainder of the scope was 3.7 mm. It had a length of 60 cm. The absence of an aspirating channel resulted in poor acceptance of this particular bronchoscope.

The authors, in conjunction with Machida America, have designed and built a new pediatric bronchoscope. The prototype which we are presently using is 3.9 mm in diameter from the tip throughout the entire working portion of the bronchoscope. The effective length (excluding control portion) is 40 cm. The weight is a mere .28 kg. The bronchoscope can only be bent at the distal tip in one direction. The angulation is limited to 90°. However, because of its light weight it can be easily rotated 360°. The lack of angulation in the opposite direction has not proven a detriment. The limitation of 90° in bending capacity is necessary because of an additional working channel. This channel permits aspiration, insufflation, biopsy, and distal grasping. The resulting aspirating channel is nevertheless satisfactory despite its very small size. An ingenious forceps has been designed to pass through the channel. Though quite small, it works well.

The channel precluded the use of cables necessary to angulate the tip in a second direction. It also necessitated a reduction in the total number of illuminating fibers. The relative loss of illumination is partially overcome with the use of a rigid bronchoscope.

The working channel further expands the capacity of this instrument to increase its versatility from other existing instruments in the nasal cavity and the nasopharynx.[1] The greatest limitation of the new bronchoscope is the size. It should be introduced through a rigid bronchoscope, an endotracheal tube of 5 mm or greater, or a number 3 "Shiley" type tracheotomy tube with an internal diameter of 4.8 mm. Its diameter allows passage through tubes no smaller than 4.5 mm inside diameter.

This bronchoscope is not intended for use in the infant, except in the nasopharynx.

Presented at the meeting of the American Broncho-Esophagological Association, Palm Beach, Florida, April 24-25, 1978.

Its greatest application will be in children over five years of age and in pediatric intensive care units. It will be of use in the assistance and management of (Pediatric COPD) chronic obstructive lung disease, i.e., cystic fibrosis. The application of the flexible bronchoscope in the adult in these latter areas is well-recognized.

In summary, this new instrument is meant to be an adjunct to the routine open tube fiberoptic lit bronchoscopes and Hopkins rod system telescopes. This new instrument will undoubtedly widen our diagnostic and therapeutic armamentarium. Continued experience with such an instrument will lead to further refinements and development.

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Reprints — John A. Tucker, MD, Hahnemann Medical College and Hospital of Philadelphia, 230 North Broad Street, Philadelphia, PA 19102.

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FIFTH BRITISH ACADEMIC CONFERENCE IN OTOLARYNGOLOGY

The Fifth British Academic Conference in Otolaryngology will be held July 22-27, 1979, at the University of Birmingham (U.K.). Master will be Sir Geoffrey Bateman, MA, FRCS. This conference has academic and scientific programs with distinguished international contributors to discuss a wide range of modern developments within the specialty.

Morning plenary sessions will be held with papers from invited speakers. Open panel discussions will be a significant feature and instructional sessions will also take place as well as audiovisual programs. Finally there will be a scientific and trade exhibition.

For further information and application forms write: V. Hammond, FRCS, 55 Harley Street, London WI, England.

Ann Otol 87:1978

SUSPENSION MICROLARYNGOSCOPY IN THE BOYCE POSITION WITH A NEW SUSPENSION GALLOWS

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The patient in whom laryngoscopy is difficult, calls for the placement of the patient's head in the optimum (Boyce) position prior to insertion of the laryngoscope. A new suspension gallows has been developed which provides for suspension of the laryngoscope with the patient in the Boyce position; this ensemble maintains stability of the laryngoscope, minimizes pressure on the maxilla and gives the best possible view of the anterior commissure.

The advent of microlaryngoscopy has facilitated both the diagnosis and treatment of laryngeal lesions.[1,2] On occasion however, situations are encountered where it is difficult to obtain an adequate, sustained view of the laryngeal structures, and in these situations microsurgery becomes difficult, if not impossible. An understanding of suspension laryngoscopy as a mechanical system has enabled the development of a new suspension gallows which makes it possible to perform endolaryngeal microsurgery in the difficult patient.

Considering suspension microlaryngoscopy from the mechanical perspective, the four major factors involved are:

1. Anatomy of oral cavity, neck and larynx.
2. Positioning of head, neck, shoulders of patient.
3. Choice of laryngoscope.
4. Choice of laryngoscope fixation device.

These factors will be considered separately, then a new approach to suspension microlaryngoscopy will be presented.

ANATOMIC FACTORS

White and Kander[3] reviewed 13 patients in whom direct laryngoscopy was difficult and analyzed the anatomic factors involved by making measurements on radiographs. All of the patients whom they analyzed had teeth. They found the most significant factors to be the posterior depth of the mandible – between the alveolar ridge immediately behind the third molar tooth and the lower border of the mandible, as well as the anterior depth of the mandible – between the tip of the lower incisors and the anterior limit of the lower border of the mandible. An increase in these dimensions made laryngoscopy increasingly difficult. These factors, in addition to the normal soft tissues, were thought to limit the ability of the oral cavity to accommodate a laryngoscope. Another important factor was the distance from the occiput to the spinous process of the first cervical vertebra; the shorter the distance the more difficult laryngoscopy was likely to be (Fig. 1). This appeared to be due to limitation of the endoscopist's ability to extend the head on the neck.

Cass et al[4] and Lewy and Brusca[5] identified a variety of factors, including a short muscular neck, receding lower

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Presented at the meeting of the American Broncho-Esophagological Association, Palm Beach, Florida, April 24-25, 1978.

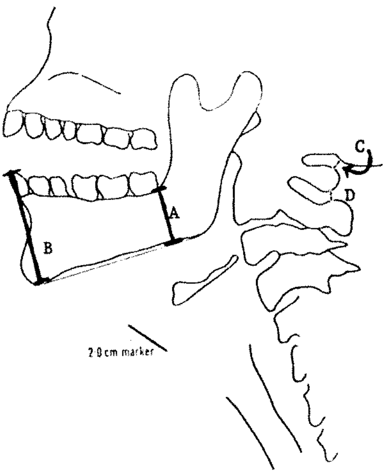

Fig. 1. Anatomic factors that tend to make direct laryngoscopy difficult.[3] A - posterior depth of mandible. B - anterior depth of the mandible. C - distance between occiput and spinous process of C1 vertebra. D - gap between the spinous processes of C1 and C2 vertebrae.

jaw, protruding upper incisor teeth, long high arched palate, and obesity, as well as cervical arthritis, that make direct laryngoscopy difficult.

After consideration of these findings and review of our own experience, it is possible to summarize the anatomic factors which make direct laryngoscopy difficult (Table 1).

All of the factors listed in Table 1 make direct laryngoscopy difficult per se, but a narrow anterior mandibular arch is very critical in microlaryngoscopy because it does not allow a wide bore binocular vision laryngoscope to take up an optimal position behind the lower incisor teeth. The sides of the wide laryngoscope may impinge on the lower premolar teeth when the anterior mandibular angle is narrow, thus making it impossible to view the anterior commissure.

TABLE 1. ANATOMIC FACTORS THAT MAKE DIRECT LARYNGOSCOPY DIFFICULT

Increase in posterior depth of mandible
Increase in anterior depth of mandible
Reduction of the distance between the occiput and the first cervical vertebra
Trismus
Protruding, long upper incisor teeth
Short, muscular neck
Marked obesity
Decreased mobility of the cervical spine, at the atlantooccipital joint
Receding lower jaw
Narrow anterior mandibular angle

It is important to bear in mind that anatomic factors make each patient different, but with recognition of the anatomic problems, an appropriate patient position, laryngoscope and suspension device can be chosen for the individual patient.

PATIENT POSITION

Chevalier Jackson said "There is no instrument made . . . that will do away with the necessity for a correct position of the patient . . .";[6] he called attention to the fact that the long axis of the trachea (and larynx) passes backward as well as downward and forward, following the general direction of the thoracic spine.

According to Jackson, the optimum position for direct laryngoscopy is one in which the patient's head is extended on the neck and the neck is flexed on the chest. Apparently this position was first described by one of Jackson's colleagues, Dr. John W. Boyce. It has become known as the "Boyce sniffing position" (Fig. 2, Position "C").

In contrast, Lewy presented an opposing view when in 1954 he wrote, "Contrary to orthodox teaching, we found no difficulty in performing laryngoscopy with the neck extended and the vertex of the head on the table...."[7]

This question of flexion versus extension of the neck is an important one. We have often found it possible to view the larynx with a patient's neck fully extended, e.g., in children, and adults without teeth; however, in many cases it is essential to incline the neck anteriorly, and extend the head on the neck in order to adequately view the anterior commissure. Suspension laryngoscopy is most successful when the optimum position of the head is obtained prior to fixing the laryngoscope in position.

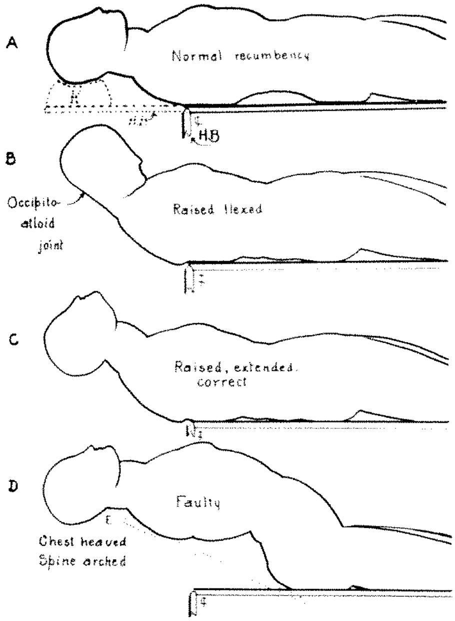

Fig. 2. Sketch made by Chevalier Jackson depicting various positions for endoscopy. Position "C" is the neck flexed, head extended, Boyce sniffing position. HB indicates the location of the movable head board on the operating table. (From Jackson[13])

LARYNGOSCOPES

The laryngoscopes that are designed to be used with the operating microscope have a wider proximal horizontal dimension that allows for binocular vision. These laryngoscopes therefore take up more room in the oral cavity. In the edentulous patient this rarely presents a problem. However, in the patient with a narrow mandibular arch the widened proximal tubular opening of these laryngoscopes (i.e., Jako-Pilling) may impair the maneuverability of the laryngoscope. The laryngoscopes most commonly utilized for microlaryngoscopy, and their features, are summarized in Table 2.

It should be noted that the laryngoscopes listed in Table 2 have handles of similar design except for the Kleinsasser laryngoscope. That is, the handles are solid metal pieces parallel to the tubular viewing portions of the laryngoscopes. Once a laryngoscope has been inserted, the proper direction of force to be exerted for exposure of the larynx is a *lifting force* exerted on the laryngoscope handle. Ideally, the force should be exerted in a direction perpendicular to the long axis of the handle (Fig. 3). This causes anterior displacement of the mandible, tongue, and supraglottic structures so that a direct line of vision from the oral cavity to the larynx is achieved, and the larynx can be viewed. When the proper view is obtained, the weight of the patient's head can be suspended by the laryngoscope blade pressing against the tongue, hyoid and epiglottis.

In devising a system where the endoscopist's hand is to be replaced by a holder, a fixation, or a suspension device, consideration must be given to the vectors of the force that are to be exerted on the laryngoscope handle to

TABLE 2. COMMONLY USED LARYNGOSCOPES

Laryngoscope	*Features*
1. Jako-Pilling	Widened proximal tubular orifice enables binocular view and bimanual instrumentation Brilliant fiberoptic illumination Well-adapted for use with the microscope Can be suspended
2. Dedo-Pilling	The slightly expanded proximal end allows semibinocular vision with improved ability to visualize the anterior commissure Adequate fiberoptic illumination Can be suspended
3. Kleinsasser	Complete binocular vision Attaches to a chest support so that the laryngoscope can be self-retained Uses the illumination from the microscope Cannot be suspended

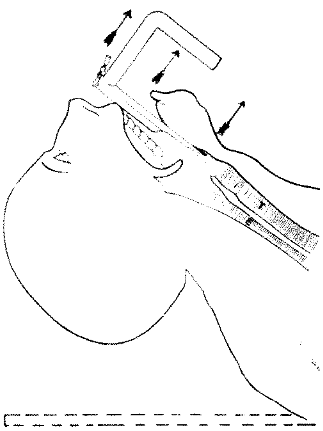

Fig. 3. Direction of lifting force to be exerted in direct laryngoscopy. Note that head is in neck flexed, head extended Boyce position. (From Jackson[13])

maintain the correct position of the laryngoscope. It should be noted that the shorter length of the solid, handle portion relative to the longer, tubular viewing portion of the laryngoscope makes it impossible to exert force at a single point on the handle that will oppose an equal and opposite force exerted at the distal end of the laryngoscope without having the laryngoscope tend to rotate. The handle must therefore be extended by the addition of a detachable extension in order to balance the forces (Fig. 4).

LARYNGOSCOPE FIXATION DEVICES

In 1909, Killian conceived the idea of maintaining a view of the larynx without having to hold a laryngoscope in position.[8] A few years later, in 1915, Lynch presented his modification of the Killian device. The Lynch suspension apparatus (Fig. 5) is composed of two parts, the laryngoscope proper, and the Killian suspension crane.

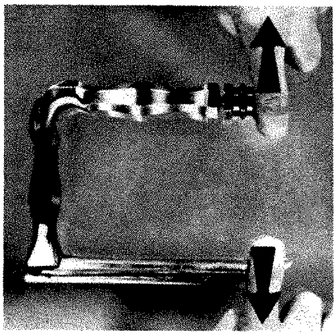

Fig. 4. A removable extension has been fitted to the handle of the laryngoscope. A force exerted near the tip of the laryngoscope can now be balanced by an equal and opposite force on the extension of the handle. The system is stable.

This laryngoscope is a functional and useful device. It enables the endoscopist to view lesions occurring in the hypopharynx and larynx while having hands free to perform a surgical procedure.[8]

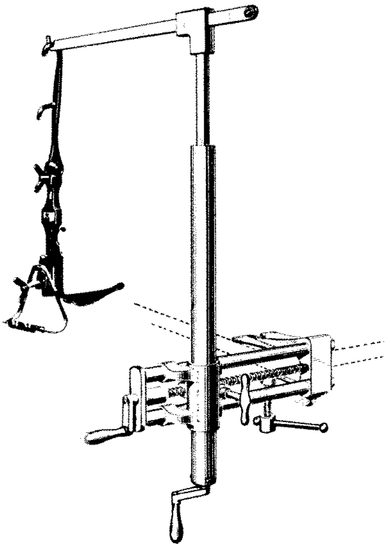

Fig. 5. Lynch suspension laryngoscope suspended from Killian gallows.

It is difficult, however, to insert the instrument and it does not afford as good a view of the vocal cords as do the modern tubular laryngoscopes.

Laryngoscope holders, on the other hand, are quick and easy to manipulate and they provide mechanical stability by using the maxilla as a fulcrum. A gear powers the upward rotation of the distal tip of the laryngoscope. The Lewy laryngoscope holder has a base that can be rested on the patient's chest so that there is no need for the gallows. Analysis of the mechanics of this system reveals that a large amount of force must necessarily be exerted on the upper teeth and a small amount of force on the chest. Though there are situations in

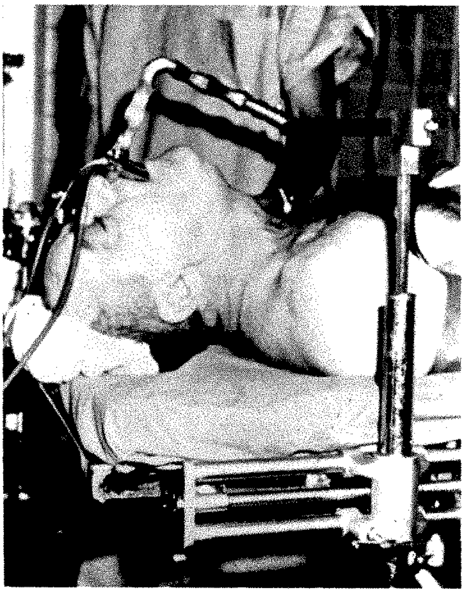

Fig. 6. The extended handle of the laryngoscope is suspended on the cross bar of the Killian gallows in the neck extended position. Note that the laryngoscope handle is not quite horizontal so that there must be some pressure on the upper gingiva in this instance.

which it is difficult to use a laryngoscope holder, the holder device usually provides adequate exposure of the larynx, especially in children and edentulous patients.

In a true suspension system, the stabilizing contact for the laryngoscope is made at a point in space anterior to the head and neck of the supine patient, thus enabling the weight of the head to be suspended on the tongue and larynx. In contrast, when the laryngoscope holder is employed, there is no vertical post in the system and it is not possible to exert a direct upward lifting force.

It has been our custom since 1968[1] to suspend the Jako-Pilling laryngoscope (fitted with an extension on the handle) from the Killian gallows whenever the larynx could be exposed with the patient in the head low and neck extended position; the laryngoscope handle would then be in the horizontal plane (Fig. 6) and little or no pressure would be exerted on the upper teeth. In difficult patients in whom the Boyce position was necessary to expose the larynx, this method of suspension could not be used because the upward force of the gallows would no longer be at a right angle to the handle of the laryngoscope.

NEW APPROACH

Realizing the problem of exposing the anterior commissure in the difficult patient, a new suspension gallows was developed which would overcome the problems inherent in the use of the Killian gallows.

The new gallows is light weight and is designed to fit the "C" clamp on the siderail of most operating room tables. It consists of a cross bar that can be raised and lowered by a worm gear and a vertical post that fits into the "C" clamp on the operating room table. The vertical post is divided into two parts and coupled together so that the upper

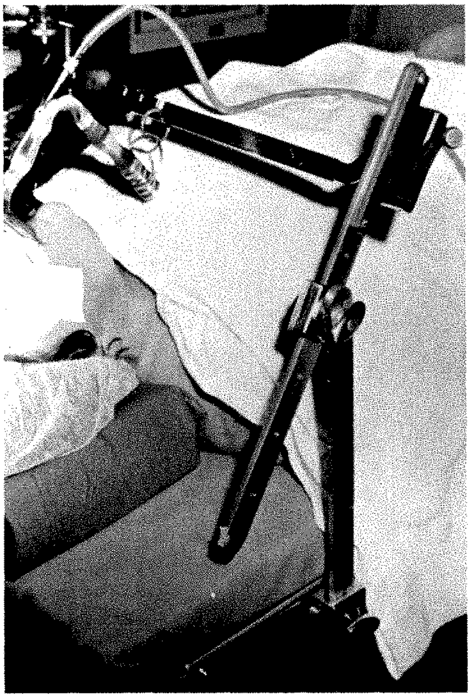

Fig. 7. The new prototype gallows is attached to the side of the operating room table. Note the inclined angle of the upper portion of the vertical post, this angle can be varied depending on the position of the laryngoscope handle.

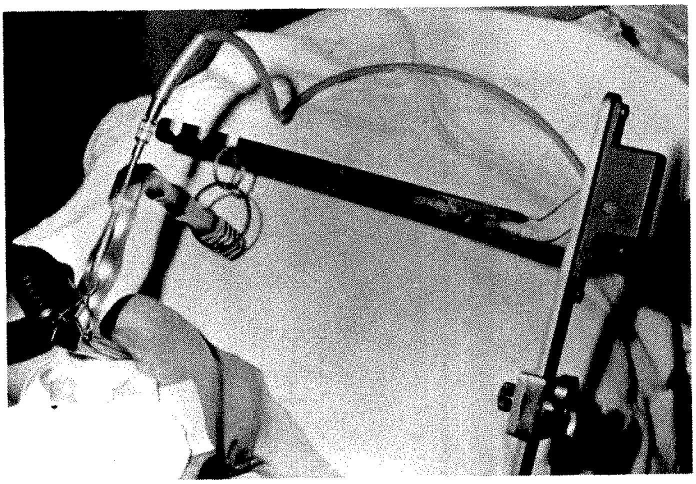

Fig. 8. Note the relation of the cross bar of the gallows to the laryngoscope handle; two rings have been interposed to demonstrate that the force exerted by the cross bar is at a right angle to the laryngoscope handle.

part, carrying the cross bar, can be deflected as much as 45° off the vertical plane. In this way the cross bar can always be raised at a right angle to the handle of the laryngoscope, whether the patient's head is extended or flexed as in the Boyce position.

The procedure is as follows:

1. Place the patient's head in the optimum endoscopic position with the neck flexed on the chest and the head extended on the neck thus raising the occiput 10 to 15 cm from the table. The head can be supported in this position frequently by the use of a conforming foam rubber pillow.

2. The laryngoscope handle is modified to accept a detachable extension,[1] or the slip-on "suspension handle" recently devised by Andrews[10] can be used.

3. Place the new suspension gallows in the "C" clamp on the side of the operating room table.

4. Position the horizontal cross bar of the gallows slightly anterior and caudal to the larynx and perpendicular to the handle of the laryngoscope.

5. Suspend the extended laryngoscope handle on the cross bar of the gallows.

In this way one can perform suspension laryngoscopy with the patient's head in an optimum position, and with minimal pressure on the maxillary teeth. The lifting force is always at a right angle to the laryngoscope handle. A prototype is shown in Figures 7 and 8.

DISCUSSION

Microlaryngoscopy offers so much to the patient in the management of his disease that it is important to extend its use to all patients whenever possible. There is no doubt that the use of wide bore laryngoscopes poses real problems in patients who present with factors that make endoscopy difficult.

However, if every possible advantage is taken of maneuvers that facilitate complete exposure of the larynx, i.e., positioning, suspension and choice of laryngoscope, microlaryngoscopy can be carried out in almost every patient. The recognition that a wide bore laryngoscope can be suspended in the optimum position, as suggested by Lynch,[8] has done much to make this possible.

The importance of the new gallows is that it directs the lifting force to maximize exposure and minimize the pressure on the maxilla. With experience, this gallows device becomes a-most as quick and easy to use as the detachable laryngoscope holder.

We have, on occasion, seen two complications during suspension laryngoscopy: namely, cardiac arrhythmias and cyanosis of the tongue with postoperative swelling of the floor of the mouth and palatine arch. Cardiac arrhythmias occurring during endoscopy should be respected and may be an indication to abort the procedure;[12] the procedure can be safely performed at a later date if appropriate precautions are taken (e.g., preoperative supralaryngeal nerve block).

Postoperative swelling of the tongue and floor of the mouth can be avoided if the tongue that becomes cyanotic during suspension is allowed to "breathe" every five minutes and allowed to become pink again. If swelling is noted postoperatively, it can be bypassed by the use of a nasopharyngeal airway because the swelling does not involve the larynx; intraoperative steroids have no effect on this type of swelling, which is probably due to venous obstruction leading to transudation of tissue fluid into the soft tissues.

From the experience we have had during the past three years, it appears that the new suspension gallows will be a very useful addition to the armamentarium of the endoscopist who does operative endoscopy and microsurgery of the larynx.

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RIGID CHEST SUPPORT HOLDER

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A rigid chest support holder used to keep the laryngoscope firmly in position during laryngeal surgery is described.

Firm support of the laryngoscope is necessary for laryngeal surgery with the CO_2 laser. Loeb[1] emphasized the importance of rigid support for conventional laryngoscopy and described ways of doing so. The "Upper Hand"* retractor holder for abdominal surgery has been modified to lock onto the straight portion of the arm of the Andrews or Lewy chest support. The curved vertical pieces are placed in the clamps on the side rails of the operating table at a convenient height above the chest and locked onto the cross bar. After the laryngeal exposure has been obtained, the chest support is rotated downward into the slot of the holder. An assistant positions the holder to meet the arm, rotates the clamp plate into position and locks with the T-handle screw. The slotted piece rotates 20° to each side in case the laryngoscope is not parallel to the long axis of the body.

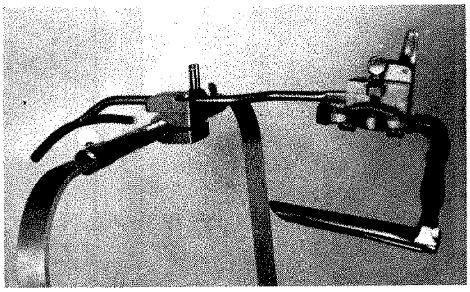

Fig. 1. "Upper hand" retractor holder modified to rigidly hold laryngoscope and chest support.

Emphasis is given to exposing the larynx by hand and using the chest support to maintain the laryngoscope position. If the screw of the chest support is advanced after placement in the holder, leverage is exerted on the upper teeth or jaw which is to be avoided.

The described holder has been found to be more convenient than the Killian gallows or other devices and to hold rigidly the laryngoscope in the desired position. Proper use avoids the problems inherent to "leverage" laryngoscopy.

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LUNG ABSCESS SECONDARY TO ESOPHAGEAL FOREIGN BODY

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The case reported here is one in which a foreign body in the esophagus resulted in a right lung abscess. Interest here centers on the unusual nature of the foreign body and the extraordinarily long period it was allowed to remain in the esophageal lumen even though it was producing symptoms throughout this period. The various factors involved are discussed, also the somewhat peculiar fact that the lung abscess was on the right, resulting from external pressure on the right main bronchus.

CASE REPORT

A ten-year-old school girl was referred from a peripheral hospital with a diagnosis of foreign body in the respiratory tract leading to lung abscess. She complained of persistent fever, dyspnea and expectoration of lots of foul-smelling sputum for five weeks. Further questioning revealed that five years earlier she had accidentally swallowed a teaspoon without handle while feeding a baby. At the time she had dysphagia only but, after this initial symptom, she had developed episodic attacks of chest pain, dyspnea, fever and cough in addition to her dysphagia for solids. The chest symptoms usually remitted following treatment at the local hospital.

On examination, she looked ill, had a temperature of 38.4 C and was obviously undernourished and clinically anemic. Finger clubbing was evident and she was mildly orthopneic. The trachea was shifted to the right. Crowding of the ribs was evident on the right side in which there were also diminished expansion, breath sounds and vocal fremitus. Other systems showed no significant abnormality.

Contributory investigations were as follows: the complete BC confirmed the clinical impression of anemia with a Hb of 6.4 gm% and HCT of 23%. The WBC was mildly elevated with a normal differential count; the platelet count was markedly abnormal and the ESR was elevated. Repeated culture of the sputum yielded only monilia. Chest x-rays showed a spoon-shaped radiopaque foreign body in the esophagus and atelectatic right main bronchus with attendant lung collapse (Fig. 1A, B).

The patient was placed on oral tetracycline and Mycostatin® as well as hematinics and, more importantly, was given intensive postaural drainage by the Physiotherapy Department. The improvement in her general condition was so rapid that after a week it was considered reasonable to subject her to a general anesthetic. Accordingly, under endotracheal anesthesia, endoscopic extraction of the metal spoon was easily accomplished. The top end of the spoon was seen at 20 cm but the rest of the spoon appeared to be buried in granulation tissue. Following extraction of the spoon there was sufficient bleeding into the esophageal lumen to prevent any further useful observation. The preoperative regimen was continued afterwards. The sputum virtually dried up within four weeks and chest x-ray (Fig. 2) showed satisfactory reexpansion of the lung.

DISCUSSION

The variety of objects found as foreign bodies in the pharynx and esophagus is remarkable and many large series appear in the literature.[1-7]

The usual assortment reported in many series includes coins, various bones, pins and nails. Statistics show

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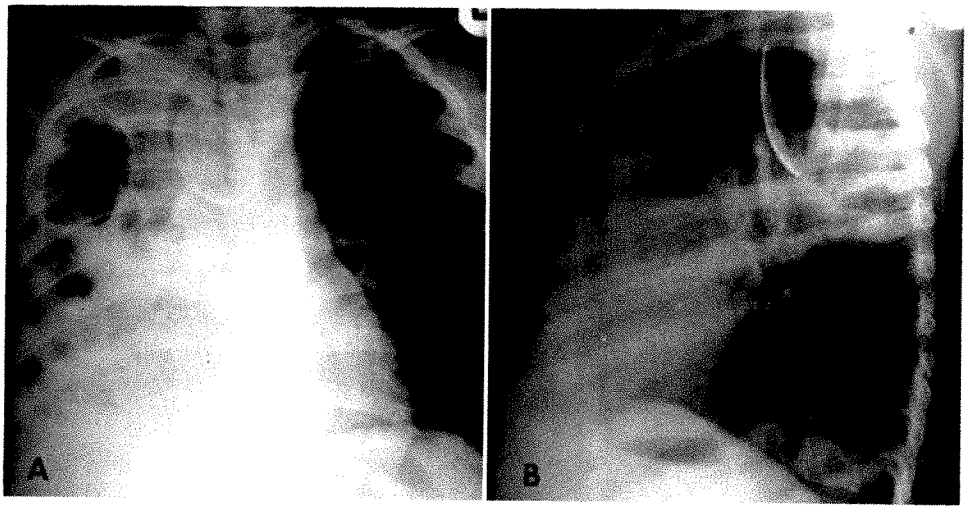

Fig. 1. A) PA x-ray of chest showing spoon in esophagus and collapse of right lung. B) Lateral chest x-ray; ballooning of esophagus is evident.

that coins and bones are the most common foreign bodies.[8] Rare foreign bodies reported in the literature include razor blades and spoon handles,[9] and recently a dead yellow jacket.[10] The author is unable to find any reference to a spoon being accidentally swallowed and impacted in the esophageal lumen except in circumstances of mental impairment.[4,9] This bizarre episode arose from the hardship imposed on ordinary people by the Nigerian civil war (1967-69) which was in progress at the time of the accident. The spoon had much earlier broken at its waist, no doubt due to metal fatigue, but the stump continued to be in service owing to the difficulty of getting a replacement during that period. It is often stated that poor children who are not given individual attention and who are left to feed themselves at an early age are more liable to swallow a foreign body.[1] In this particular case, however, it was the war situation that made it necessary to charge a five-year-old child with the sole responsibility of looking after a baby. Also the rampant deprivation of the times provided the temptation to snatch a few spoonfuls of the baby's food and the indecent hurry to avoid discovery led to the accident.

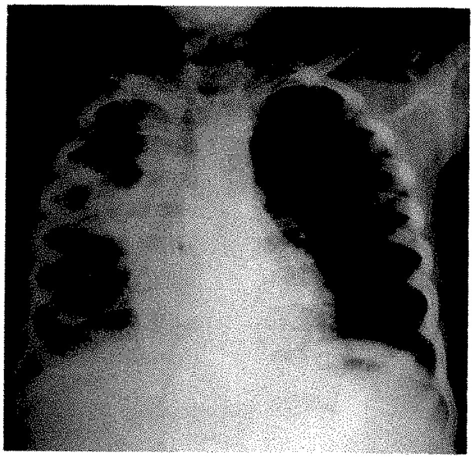

Fig. 2. PA x-ray of chest after four weeks, showing substantial reexpansion of lung.

Another unusual aspect of this case is the long period of residence of the foreign body in the esophageal lumen. Foreign bodies in the air and food passages usually give rise to dramatic symptoms and the patients seek help promptly.[11] On occasion, however, especially in children, foreign bodies in the throat are found accidentally on routine radiography or during investigation of some chronic symptom.[12-14] In these cases the foreign body has usually been present for many weeks or months. The present author is unable to find any report in the literature of a foreign body being present in the esophageal lumen for as long as five years, notwithstanding that it was producing symptoms throughout this period. The factors responsible for the long delay in this case are varied and interesting. It would appear that the patient did not at first reveal the cause of her symptoms to her parents, no doubt because of the circumstances in which the accident occurred. Another factor in this long delay was again due to the civil war which made it impossible to seek early help once the correct history was obtained from the patient. Even so, it took more than four years from the end of the civil war before the patient was seen in this unit. It is a regrettable fact that in some cases of foreign body in the food and air passages a lot of delay in getting proper medical care is due to physicians ignoring the history of ingestion of foreign bodies.[11,14]

Chest complications following impaction of foreign body in the pharynx or esophagus are not uncommon. This is usually due to aspiration of saliva or food into the chest, as a result of pooling above the foreign body. External pressure on the trachea or bronchial tree may lead to lung collapse and possibly lung abscess. Anatomical considerations would make it a lot more likely for the left main bronchus to be so compressed. In the present case the right main bronchus was involved and it would appear from Figure 1A and B that the spoon ballooned the esophageal wall well to the right and so compressed the right main bronchus.

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ELECTROCOCHLEOGRAPHIC STUDY OF SUDDEN DEAFNESS

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By performing electrocochleography (AP, SP and CM) on 34 patients with sudden deafness, it was thought that the pathophysiology of this disease could be deduced. The various waveform patterns of AP and SP responses obtained in cases of sudden deafness were classified into the following types: 1) AP high response; 2) decreased AP high response; 3) AP low response; 4) dominant −SP; 5) −SP or +SP; and 6) AP, SP no response. The cases showing the type of dominant −SP and AP high response had satisfactory prognoses. In these cases the sensory epithelium and the cochlear nerve seemed to indicate a reversible condition being affected by the temporary functional block. Furthermore, it seemed to indicate that the neural regions related to the source of AP(N_1) response were impaired in cases in which CM were recorded at normal response threshold in spite of the absence of AP(N_1) response. In the unsatisfactory prognosis cases with decreased AP high response, AP low response and AP, SP no response in which only the extremely low or depressed CM responses could be recorded, it seemed that the sensory epithelium and the cochlear nerve were affected permanently, although the degree of impairment varied.

Clinical electrocochleography (ECochG) which nonsurgically records such electrical activity from the human cochlear and first-order neurons as auditory nerve action potentials (AP), cochlear microphonics (CM) and summating potentials (SP), has been applied in the testing of auditory acuity objectively in patients who cannot cooperate in other methods of hearing assessment, and has recently been used as a method of determining the pathology underlying auditory dysfunction.

A preceding paper[1] reported that ECochG can be an effective means for judging the prognosis of sudden deafness at the initial stage of onset. In this study the pathophysiology of sudden deafness was studied by ECochG.

SUBJECTS AND METHODS

The subjects of this study were 34 patients with sudden deafness who visited the outpatient clinic of the Department of Otorhinolaryngology, Nagasaki University School of Medicine, during the period from April 1975 to March 1976.

Subjects, resting comfortably on a couch, were tested in an electrostatically shielded room. The active electrode was a thin stainless steel needle, 0.2 mm in diameter, enameled except at the tip which was pointed. This electrode was passed through the tympanic membrane and rested on the promontory close to the round window recessus. A reference electrode was placed on the ipsilateral ear lobe and a ground electrode on the forehead. The recording electrode was connected by shielded low noise cables to a wide band differential preamplifier.* The amplified signals were then routed to a bandpass filter with a filter setting of 5 Hz to 10 kHz and summed up by a computer averager.** Averages varied from 50 to 500, according to the signal-to-noise ratio of the response in the ongoing background activity. The averaged response was recorded on paper by an X-Y recorder.

The acoustic stimulation used for the measurement of AP and SP was a click, produced by sine wave of one cycle (duration 0.25 msec). The frequency components of this click were relatively even, so as to contain wide frequencies below 4 kHz without any definite central component. Click stimuli were alternated in polarity to prevent the appearance of CM in the average response. Short tone bursts of 3 msec duration at 2 kHz, 4 kHz and 8 kHz, and 6 msec duration at 0.5 kHz respectively with 1 msec rise-decay time were used for the measurement of CM. Both types of stimuli passed through power amplifiers and attenuators. They were given from a

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*Model AVB-2, Nihon Koden, Tokyo, Japan.

**Model ATAC 201, Nihon Koden, Tokyo, Japan.

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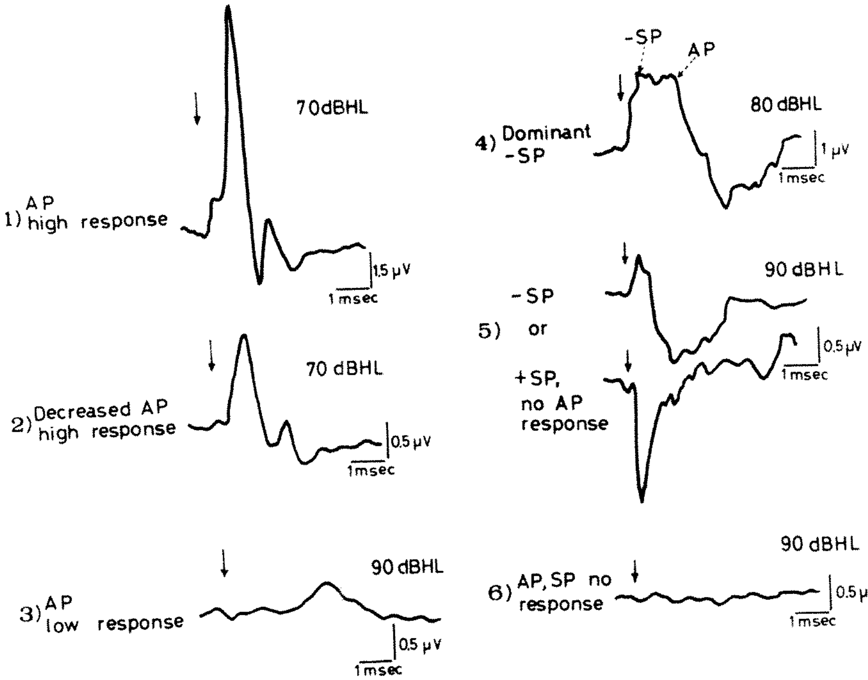

Fig. 1. Various waveform patterns of AP and SP responses obtained from ECochG in patients with sudden deafness.

TABLE 1. CRITERIA FOR DIAGNOSIS OF SUDDEN DEAFNESS

A. Conditions

1. Sudden hearing loss: Deafness may begin instantaneously or be first noticed by the patient on awaking in the morning, but the patient should be able to state what he was doing when hearing loss occurred, i.e., "sleeping" or "working," etc.
2. Profound sensorineural hearing loss: The degree of hearing impairment is not always profound, but many patients notice sudden hearing loss only when it is severe.
3. Unknown cause or uncertain cause: Cause is not manifest.
4. Tinnitus: Tinnitus is often associated with the onset of hearing loss.
5. Vertigo, nausea and vomiting: Some patients have vertigo, nausea and vomiting at about the same time as the onset of hearing loss but do not have repeated attacks.

B. Diagnostic Criteria

I. Diagnosis *definite*: conformable to all conditions 1), 2), 3), 4) and 5).

II. Diagnosis *suspicious* or *uncertain*: conformable to 1) and 2).

shielded loudspeaker located 50 cm lateral to the tested ear and repeated at a rate of five per second. The level of these stimuli is measured in decibels above their normal human hearing threshold (hearing level: HL). For the click and tone bursts, 0 dB HL corresponds to 23 dB and 27 dB respectively above 0.0002 dynes/cm^2 (peak equivalent SPL).

The method of diagnosing sudden deafness and the degree of hearing improvement were determined on the basis of the criteria established by the Sudden Deafness Research Team of the Ministry of Health and Welfare of Japan. The criteria of diagnosis are shown in Table 1. The criteria of the degree of hearing improvement are as follows: 1) complete recovery: recovery to within 20 dB of normal hearing at each frequency of 0.25, 0.5, 1, 2, and 4 kHz or improvement to the same degree of hearing as the normal ear; 2) remarkable improvement: improvement by more than 30 dB in the arithmetic mean of the previously mentioned five frequencies; 3) slight improvement: improvement by 10 to 20 dB in the mean of the five frequencies; and 4) no change: change within ±10 dB in the mean of the five frequencies.

Electrocochleogram of Sudden Deafness. In this study the various waveform patterns of AP and SP responses obtained in 34 patients with sudden deafness were classified into the following six types (Fig. 1): 1) AP high

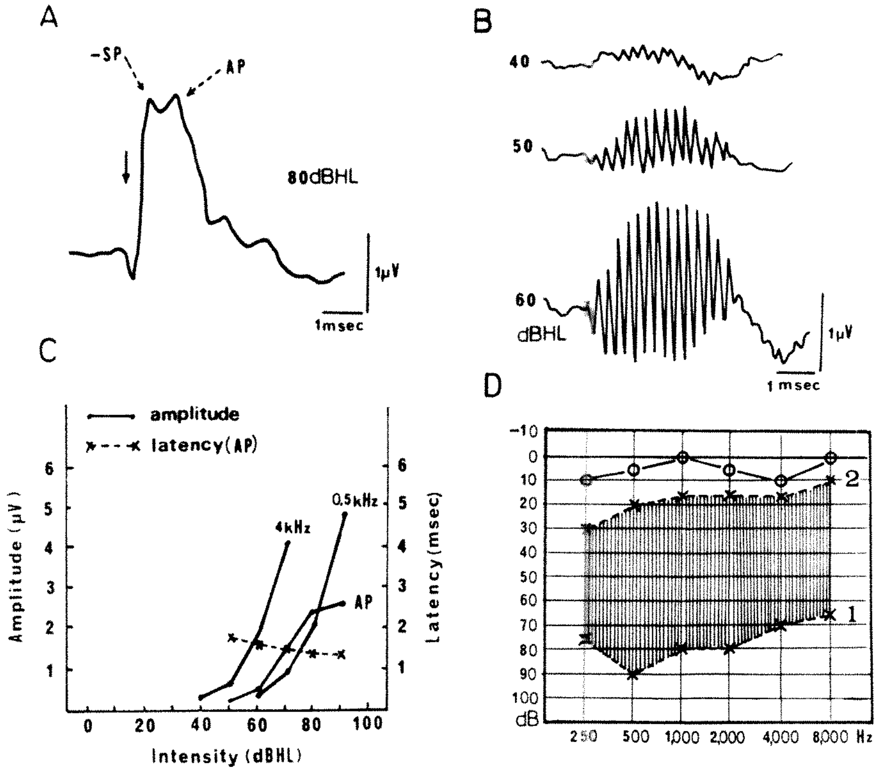

Fig. 2. (Case 1) A) ECochG at the first examination shows dominant −SP type. B) CM responses at 4 kHz are recorded from the threshold of 40 dB HL and the potential increases systemically with stimulus intensity. C) Input-output functions of AP and CM response. D) Pure tone audiogram: 1 indicates results at first examination, three days after onset, and 1 shows results 27 days after onset.

response, 2) decreased AP high response, 3) AP low response, in which the AP showed peculiar changes in magnitude or input-output functions, 4) dominant −SP, 5) −SP or +SP, in which SP indicated singular response in magnitude or change in polarity, and 6) AP, SP no response. Figure 1 shows one of the waveforms of each type dealing with the click intensity described in the figure.

1. AP high response: AP response has a greater amplitude or one almost equal to that of the normal subject in the H-part and an absence of the L-part. The increment of AP amplitude is steeper with increasing intensity in input-output functions.

2. Decreased AP high response: AP response has a decreased AP amplitude in the H-part and is absent in the L-part. The increment of AP amplitude is minimal with increasing intensity (input-output curve of AP amplitude shows a gradual slope, see Fig. 5 A, B)

3. AP low response: Even at the maximum sound intensity of 90 to 100 dB HL, AP response shows a delayed latency as seen in the L-part in subjects with normal hearing and a low output potential.

4. Dominant −SP: The dominant −SP has an amplitude almost equal to that of AP or a voltage much higher in the H-part than that of the normal subject (Fig. 2 A).

5. −SP or +SP: The waveforms of only the SP response have a negative or positive deflection that develops im-

TABLE 2. ELECTROCOCHLEOGRAPHIC FINDINGS IN SUDDEN DEAFNESS (N = 34)

Prognosis	*Waveform Pattern*	*Cases*	*CM Threshold (4 kHz) dB HL* 40	50	60	70	80	*Artifact Level*	*Total No. of Cases*
Satisfactory	Dominant −SP	8	1	2	1		1		5 (3)*
	AP high response	7		5	2				7
Unsatisfactory	Decreased AP high response	2				1		1	2
	AP low response	2							(2)*
	−SP or +SP no AP response	6	1			1		4	6
	AP, SP no response	9		1		1		5	7 (2)*

*Figures in parentheses represent the number of cases without CM measurement.

mediately after the start of CM. No AP response is obtained.

6. AP and SP no response: The waveforms show neither AP nor SP response, even at the maximum sound intensity.

Among the above six categories, complete recovery or remarkable improvement in the hearing was seen in Types 1 and 2, slight improvement or no change in Types 3, 4 and 5.

Table 2 shows various waveform patterns and prognoses of 34 patients with sudden deafness. Dominant −SP was seen in eight cases and AP high response in seven cases, and the cases of these two types showed satisfactory prognoses. In 11 of the 12 cases with such satisfactory prognosis waveform patterns as dominant −SP and AP high response for whom CM determination at 4 kHz was performed, the CM responses were recorded at normal response threshold.

On the other hand, decreased AP high response was seen in two cases, AP low response in two cases, −SP or +SP in six cases, and AP, SP no response in nine cases, all of which showed unsatisfactory prognoses. In 10 of the 15 cases with these waveform patterns for whom CM determination was performed, only the extremely low or depressed CM responses could be recorded. However, in one case each of −SP type and AP, SP no response type, CM appeared in response to a sound intensity of 40 to 50 dB HL, and the voltage increased systemically with increasing sound intensity.

CASE REPORTS

IMPAIRED REGIONS OF SUDDEN DEAFNESS AS DEDUCED BY ELECTROCOCHLEOGRAPHY

Temporary Functional Impairment of Sensory Cells and Auditory Nerve

Case 1. Sudden deafness developed in the left ear of a 32-year-old female (Fig. 2). At first examination on the third day after onset, she had no dizziness and results of a caloric test were normal. The pure tone audiogram showed a horizontal pattern with a mean of 82 dB. The ECochG demonstrated an AP amplitude of approximately 2μV and −SP of voltage nearly equal to that of the AP at the sound intensity of 80 dB HL, which fit the category for the dominant −SP waveform. The threshold of AP response was 50 dB HL. CM responses at 4 kHz and 0.5 kHz were recorded from the threshold of 40 dB and 60 dB HL respectively, and the potentials increased systemically with stimulus intensity. This patient completely recovered within 27 days after the onset of hearing loss.

Comment: All patients with sudden deafness who showed AP high response or dominant −SP waveforms in the ECochG performed at an early stage of onset demonstrated complete recovery or remarkable improvement. Their electrocochleographic findings included many instances of satisfactory CM output. Therefore, it was unlikely that the hair cells and auditory nerve were impaired organically in the cases showing such an ECochG, but it was conjectured that the sensory cells and auditory nerve were in a condition of temporary functional block due to some reversible physical or chemical change at the neural level or in the endolymphatic space.

Impairment at the Neural Level

Case 2. Sudden deafness developed in the

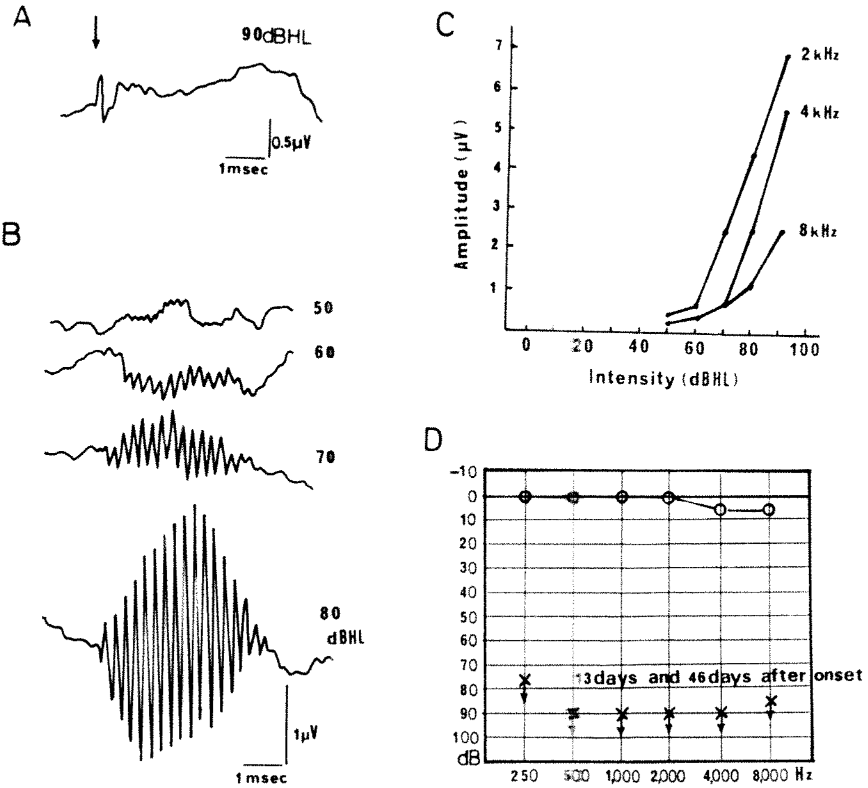

Fig. 3. (Case 2) A) ECochG at the first examination shows AP, SP no response type. B) Normal-looking CM response is recorded by tone-bursts of 4 kHz. C) Input-output functions of CM response at 2, 4, and 8 kHz. D) Pure tone audiogram at 13 and 46 days after onset.

left ear of a 16-year-old boy (Fig. 3). At first examination on the 13th day after onset, there was no evidence of dizziness, and results of the caloric test were normal. The pure tone audiogram showed total hearing loss and no improvement after a lapse of 46 days. In the ECochG at first examination, neither AP nor SP was recorded in response to a sound intensity of 90 dB HL. However, the threshold for the CM response at 2, 4 and 8 kHz was 50 dB, 50 dB and 60 dB HL respectively, which was almost equal to that of the normal subject, and well-developed CM outputs were obtained at all levels. In this case herpesvirus was identified from the cerebrospinal fluid.

Case 3. A 6-year-old boy was first examined about two months after the occurrence of mumps because his parents suspected deafness (Fig. 4). The pure tone audiogram showed total hearing loss in the left ear. The waveform recorded at sound intensity of 80 dB HL showed only positive and negative SP. But the threshold for the CM response at 0.5, 2, 4 and 8 kHz tonebursts was 70 dB, 50 dB, 50 dB and 50 dB HL respectively. Satisfactory CM output was obtained in the input-output functions of CM responses.

Comment: Electrocochleographic findings in Case 2 (Fig. 3) were quite similar to that of mumps deafness as seen in Figure 4 in which the ECochG showed a normal-looking CM response despite the absence of AP response. Since CM responses were satisfactory in such cases, it was unlikely that the hair cells were impaired very seriously. Accordingly, it was thought that some instances of sudden deafness had the region of impairment only at the AP (N_1) level of the auditory nerve or that cases of auditory impairment could exist only at the neural level.

Organic Impairment of Sensory Cells or Auditory Nerve

Case 4. Sudden deafness developed in the right ear of a 47-year-old male (Fig. 5). At first examination on the third day after onset, there was no evidence of dizziness, and the caloric test gave negative results. The pure tone

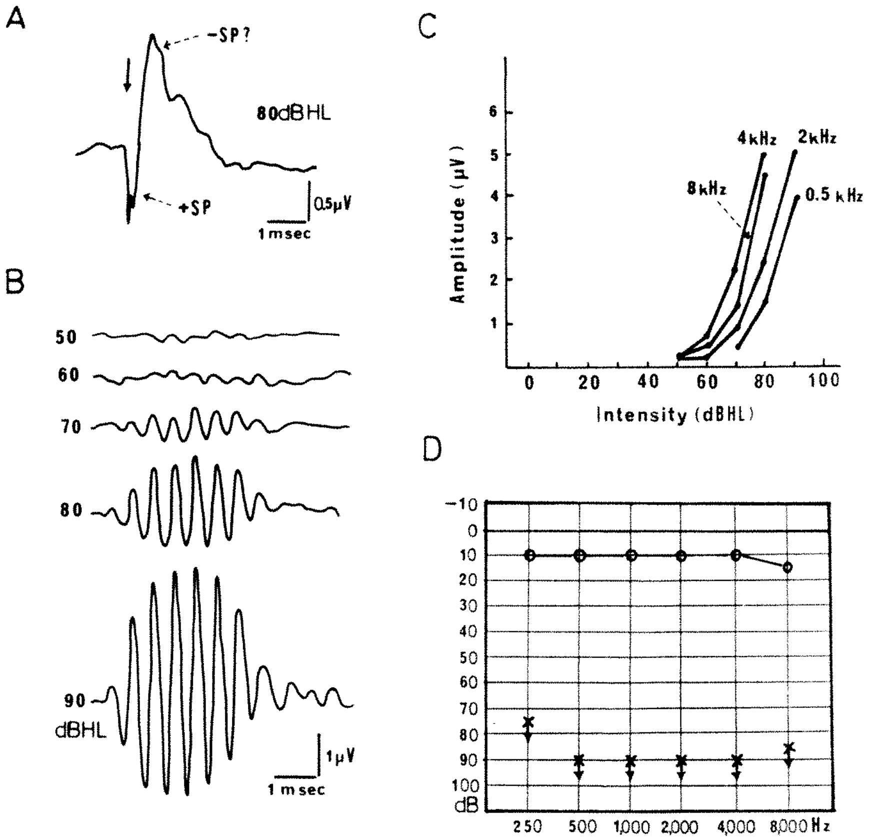

Fig. 4. (Case 3) A) ECochG shows only positive and seemingly negative SP response with no AP response. B) Normal-looking CM response is recorded by tonebursts of 2 kHz. C) Input-output functions of CM at 0.5, 2, 4 and 8 kHz. D) Indicates pure tone audiogram.

audiogram at that time indicated intermediate sensorineural deafness at a mean of 56 dB, suggesting a relatively satisfactory prognosis. However, there was hardly any improvement in the patient's hearing after a lapse of 50 days. In the ECochG, a waveform of AP appeared in response to sound intensity of 60 dB HL, but the output voltage of AP in response to 90 dB was low. The input-output curve showed an absence of L-part and a minimal increase of amplitude in the H-part as sound intensity increased (decreased AP high response type). The threshold for the CM response at 4 kHz was 70 dB HL, and a notably low CM output was recorded in response to sound intensity of 80 dB HL.

Comment: For all patients with slight improvement or no change, waveforms of either AP low response, decreased AP high response, only negative or positive SP or AP, SP no response with the extremely depressed CM responses were obtained in the ECochG at first examination. In cases showing such ECochG, it was speculated that severe organic impairment, including the hair cells or auditory nerve, was present and as a result, prognoses were considered to be unsatisfactory.

DISCUSSION

In patients with sudden deafness, various patterns of pure tone audiograms are observed at the time of stability of hearing. In fact Schuknecht,[2] Beal et al[3] and Lindsay[4] reported pathologic findings in which the severity of the condition of the inner ear and the auditory nerve varied from mild to pronounced impairment. However, the pathology reported by them, of course, represents the final stage of these processes in patients in whom spontaneous

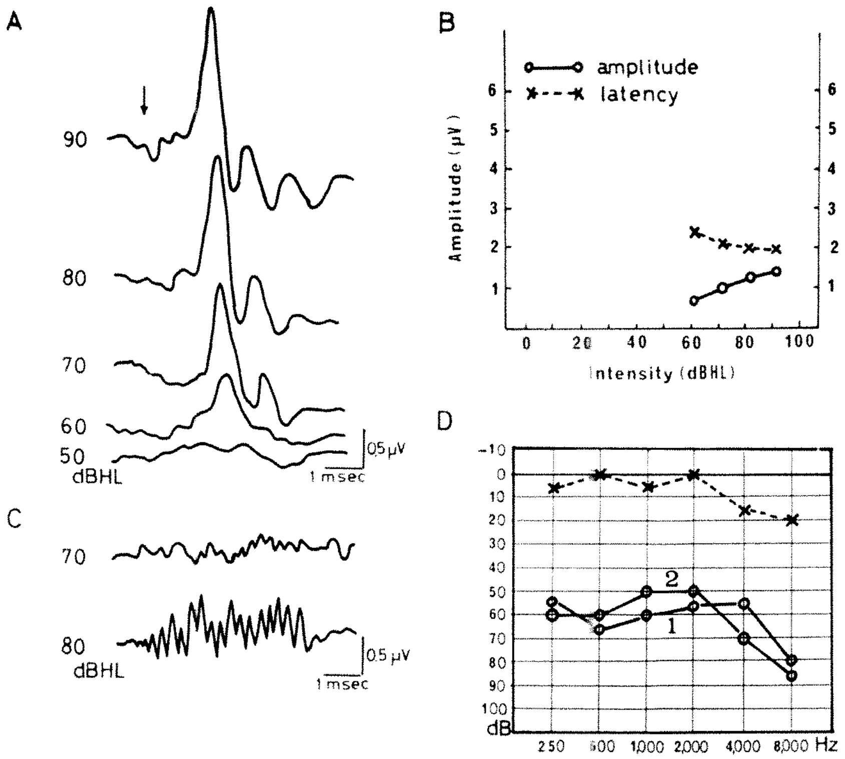

Fig. 5. (Case 4) A) ECochG at the first examination shows decreased AP high response type. B) AP input-output functions are shown. Amplitude of AP increases more minimally with increasing intensity. C) CM response to tonebursts of 4 kHz are shown. A notably low CM output is recorded. D) Pure tone audiogram; 1 indicates results at first examination, three days after onset, and 2 shows results 50 days after onset.

recovery did not occur.[5] Therefore, their findings do not represent the outcome in all cases.

The results of our study demonstrate a definite electrocochleographic difference between types which indicate a satisfactory prognosis and those that predict an unsatisfactory prognosis. Particularly in view of the fact that all patients that had dominant −SP or AP high response type with satisfactory CM output in their ECochG had complete recovery or remarkable improvement after a relatively short period, these findings seem to show that there is no permanent change in inner ear pathology.

Ishii et al[6] have reported cases of sudden deafness with minimal changes in the organ of Corti though the cochlear nerve was completely lost. These cases may be equivalent to those with impairment at only the neural level as judged from our electrocochleographic findings, suggesting that the retrocochlear route of impairment is possible in sudden deafness. The electrocochleographic findings which seemed to indicate a lesion at only the neural level were obtained in some instances of mumps deafness.

In reviewing the etiology of sudden deafness, many causes, such as viral agents, vascular causes, allergic factors, etc, have been shown, but the etiology is not sufficiently known. However, virus infection of the inner ear is thought to be one of the common causes of sudden sensorineural deafness. In our study, herpesvirus was verified in one of the cases which was suggestive of retrocochlear lesion in electrocochleography. In considering the viral agents as the etiologic agents of sudden deafness, it is speculated that impairment at the neural level suggests viral neuronitis and ganglionitis, while decreased AP high response, AP low response and AP, SP no response with depressed CM response suggest both viral endolymphatic labyrinthitis and neuroganglionitis as the result of the impairment in the region from the retrocochlear toward the cochlear, although the degree of impairment may vary.

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IMMUNOBIOLOGY IN OTOLARYNGOLOGY

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Immunologic aspects of otolaryngologic diseases are appearing in our literature, and clinical applications of these concepts are becoming available. The significance of these advances is obscured by the confusing terminology usually employed; however, the terminology can be mastered without much difficulty. The humoral and cellular divisions of the immune system have long been recognized. The humoral division of the immune system appears to play a major role in the prevention of infection, autoimmune disease, and atopic disease. The cellular division is probably most important in the prevention of neoplastic disease. There is overlap and the systems do interact. Future manipulations of the immune system may assist in the diagnosis and treatment of diseases such as chronic secretory otitis media, allergic rhinitis, and cancer of the head and neck.

Immunologic concepts are appearing in our literature in increasing frequency dealing with diseases such as chronic secretory otitis media, allergic rhinitis, and carcinoma of the head and neck. Clinical applications of these concepts are becoming available, and it is incumbent upon us as physicians to make these advances available to our patients. Unfortunately, much of the work done in immunobiology today is reported in experimental journals and is further obscured by a considerable amount of confusing terminology. It is the purpose of this paper to demonstrate that the basic concepts of immunobiology are neither complicated nor new and the confusing terminology can be mastered without much difficulty.

The foundations for modern day immunology were laid in 1798 when Jenner discussed active immunization against smallpox,[1] and in 1890 when Koch described the cutaneous hypersensitivity reaction in patients with tuberculosis.[2] These milestones, which dealt with the humoral and cellular divisions of the immune system respectively, are as relevant today in understanding the immune system as they were a century ago.

FUNCTIONAL DEFINITION OF IMMUNE SYSTEM

Maintenance of the body's integrity is the principal function of the immune system. The immune system has evolved mechanisms which destroy invaders of extrinsic origin (virus, bacteria, and various parasites) as well as invaders of intrinsic origin (neoplastic cells). The immune system occasionally will dysfunction, and its mechanisms will attack normal cells and/or structures, resulting in autoimmune disease.

The immune system is composed of two divisions: humoral immunity (immediate hypersensitivity) and cell-mediated immunity (delayed hypersensitivity). Humoral immunity is mediated by B-lymphocytes and may be transferred via cell-free plasma. Cellular immunity is mediated by T-lymphocytes. Transferral of cellular immunity requires the actual transfer of T-lymphocytes. Antigen may activate either or both of these divisions.

The functional division of the immune system is best understood by ex-

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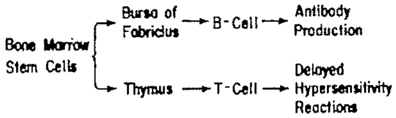

Fig. 1. Diagrammatic representation of the development and function of the humoral and cellular divisions of the immune system. The bursal equivalent in man has not yet been localized.

perimental data on the chicken. The chicken has two primary lymphoid organs, the bursa of Fabricius and the thymus. The bursa of Fabricius is responsible for converting a population of lymphopoietic stem cells from the bone marrow into B-lymphocytes. The thymus is responsible for converting another population of lymphopoietic stem cells into T-lymphocytes. If the bursa is removed from the neonatal chicken, there is an absence of circulating antibodies, but cell-mediated immunity remains intact. If the thymus is removed, cell-mediated immunity is impaired although antibody levels are near normal. Human counterparts to these experimentally induced states have been described.

Bruton's agammaglobulinemia is seen in human infants suffering from a congenital sex-linked disease, and it represents a human correlate of the condition induced in the chicken by neonatal removal of the burst of Fabricius. These children are unable to produce antibodies in response to antigenic stimulation and are more susceptible to a wide variety of infectious diseases. Gamma globulin therapy is dramatically effective in some children, although this condition is not completely curable and a tendency toward infection persists. The human equivalent to the bursa of Fabricius is believed to be the gut-associated lymphoid tissue, particularly Peyer's patches.

DiGeorge's third and fourth pharyngeal pouch syndrome is a clinical example of total thymic aplasia. These patients are unable to produce a cell-mediated immune response. They present with leukopenia, normal concentrations of plasma cells, and immunoglobulins in near normal concentrations. Since there are many pathogenic bacteria and several protozoan parasites that are unaffected by immunoglobulins, children with this disorder are also susceptible to various infections. The parathyroid glands are also missing in these patients and, therefore, they exhibit other metabolic abnormalities. Thymus transplants are now being performed in an attempt to establish cell-mediated immunity in these patients. This syndrome represents the human equivalent of the neonatally thymectomized chicken.

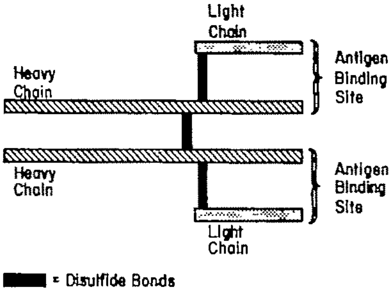

Fig. 2. Basic immunoglobulin structure.

The Swiss type of lymphopenic agammaglobulinemia represents a defect in the production of lymphopoietic stem cells. These children fail to develop lymphoid tissue and have neither humoral nor cell-mediated immunity. Prognosis is, of course, extremely grave although immunologic reconstruction is currently being attempted.

In summary, the function of the immune system is under two control centers: 1) the bursal equivalent in man which controls humoral immunity production, and 2) the thymus which controls cell-mediated immunity. These systems are outlined in Figure 1.

HUMORAL IMMUNITY (B-LYMPHOCYTE SYSTEM, IMMEDIATE HYPERSENSITIVITY)

The two main components of the humoral immune system are antibody and complement. Antibodies are a series of proteins located in the gamma globulin fraction of serum proteins and are defined by their specific structure. This structure consists of two heavy and two light polypeptide chains, which are con-

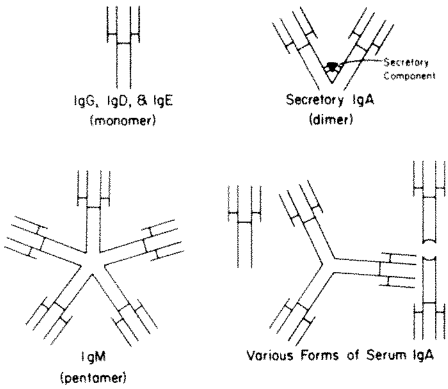

Fig. 3. The structure of the immunoglobulins.

nected by disulphide bonds (Fig. 2). Immunoglobulin can exist as monomers, dimers, trimers, or pentomers of this basic immunoglobulin subunit. IgG, IgE, IgD, and some IgA exist primarily as monomers. IgA also exists as a dimer and a trimer, and secretory IgA exists as a dimer with glycoprotein connecting piece. IgM exists as a pentomer. These structures of the five classes of immunoglobulins are illustrated in Figure 3. Antibodies are immunologically active immunoglobulins.

Complement is the second component of the humoral system; and, once activated by certain classes of antibodies, complement cascades to a powerful destructive force. There are nine separate complement components. These complement components undergo a specific series of reactions known as complement fixation when activated by IgM or IgG.

If antibody capable of activating complement is produced against normal cells or structures, severe autoimmune disease results. Autoantibodies have been documented in autoimmune hemolytic anemia, Hashimoto's thyroiditis, and in Goodpasture's syndrome. Poststreptococcal glomerulonephritis appears to be the result of complement activating antibodies bound to glomerulus antigens. An acute inflammatory response is initiated within the glomerulus and the clinical sequelae of acute glomerulonephritis thereby result.

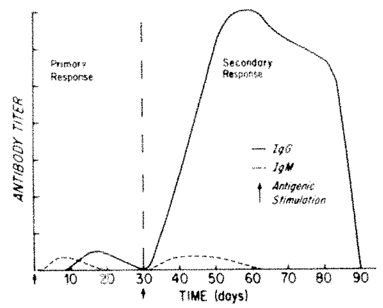

Fig. 4. The primary and secondary response of antibody production.

An *antigen* is any molecule which can elicit either a humoral or cellular immune response. Although one system usually predominates, both types of lymphocytes are stimulated to some degree by the antigen. There are specific antigens situated on the membranes of tumor cells which are produced by the tumor cell. These "tumor antigens" are also frequently released into the general circulation. Detection of these tumor antigens may allow for the early diagnosis of the presence of carcinoma.

Antibody Production. When an antigen is introduced into the body, it is phagocytized and processed by macrophages. The antigens are then "presented" to either the B-lymphocyte or a T-lymphocyte by the macrophage. Twenty-four to 48 hours after the initial exposure of the B-lymphocyte to antigen, low levels of antibodies (primarily IgM) are produced. This antibody production is referred to as the *primary humoral response.* If the same antigen is reintroduced at a later date, high levels of IgG are demonstrable within 24 hours. This antibody response to the reintroduction of antigen is referred to as the *secondary humoral response* (Fig. 4). The functions of antibody in the humoral response are diverse; however, it appears that each class of immunoglobulin has its own primary functions.

Functions of Immunoglobulin G (IgG). IgG is the only immunoglobulin that is able to cross the placenta and is important in protecting the newborn. IgG is the predominant antibody class of the secondary humoral response and is able to activate complement. It is an important immunoglobulin in protecting the body's hemostasis; however, it may also participate in autoimmune diseases. IgG is also important in opsonizing antigens, so that the antigen may be more easily phagocytized by macrophages.

Functions of Immunoglobulin M (IgM). IgM is the major component of the primary humoral response and is able to activate complement with greater avidity than IgG. Together IgG and IgM may serve as specific antitoxins against bacterial or other toxins such as diphtheria, tetanus, botulism, gangrene, snake venoms, and anthrax.

Functions of Immunoglobulin A (IgA). IgA is of particular interest to us as otolaryngologists as it is the primary immunoglobulin of the mucosal immune system.[3] There is a preponderance of IgA-producing B-lymphocytes in the submucosal regions of the respiratory and gastrointestinal tracts. The mucosal immune system is an extensive immune organ which is the first line of defense against invasion by potentially pathogenic microorganisms and viruses.

Two forms of IgA have been documented, serum IgA (IgA) and secretory IgA (sIgA). Secretory IgA is the predominant class of immunoglobuli in the saliva, tears, and secretions of the respiratory and gastrointestinal tracts. Although it does not activate complement, sIgA is capable of neutralizing a wide variety of respiratory viruses. There is, however, little or no resultant systemic immunity unless the pathogen crosses the mucosal barrier and induces a viremia.

Secretory IgA also impedes the absorption of soluble antigens through mucosal surfaces. Patients with selective IgA deficiency frequently have circulating antibodies to food antigens, such as milk proteins,[4] and selective IgA deficiency is significantly more common among allergic patients.[5] It appears that a systemic humoral immunity can develop against common antigens if sIgA does not prevent their crossing the mucosal barrier. Conversely, selective IgA elevations have been noted in patients with carcinoma of the head and neck.[6] It is conceivable that this elevation of IgA could impair the host response against neoplasia.

Study of the mucosal immune system and possible immunologic function of the tonsils have also recently received attention. Tonsillectomy has been noted to produce a modest reduction in secretory antibody titers against poliovirus in previously immunized children. Moreover, a less vigorous response to primary local immunization with live polio vaccine has been seen in tonsillectomized patients.[7] Whether these observations were caused by the absence of tonsils or the presence of the disease for which the tonsillectomy was performed are questions which deserve our consideration.

Functions of Immunoglobulin D (IgD). Serum IgD concentrations are very low and functions have not yet been clarified.

Functions of Immunoglobulin E (IgE). Serum concentrations of IgE are extremely low; however, one of its functions has recently been well established. Serum IgE has been implicated in the etiology of *atopic disease.* An atopic patient is an individual suffering from what we commonly think of as allergic disease. These reactions may include allergic extrinsic asthma, allergic rhinitis, hay fever, urticaria, atopic dermatitis, or anaphylactic shock. These diseases are associated with elevated levels of serum IgE. IgE mediates allergic reactions in which histamine and histamine-like substances are released and the above clinical syndromes are noted. Serum IgE levels may prove to be helpful in distinguishing allergic or atopic disease from infectious disease. Parasitic diseases are the only infectious illnesses which produce elevated serum IgE levels.

It has been suggested that IgE-associated hypersensitivity mechanisms may be involved in the pathogenesis of chronic secretory otitis media[8] and allergic rhinitis.[9] Demonstration of elevated serum IgE levels does not specify the offending allergic agent, but it may be of value in identifying patients with an allergic etiology to their disease. Tests are also available which can demonstrate how much of the IgE elevation is directed toward some of the more common allergic agents. These diagnostic techniques are becoming more available and may prove to reduce both money and time expenditure in the work-up of the allergic patient.

Although the role of IgE in allergic disease has been well-established, numerous investigators have questioned the positive evolutionary motivation for the development of an IgE system. Does the IgE system exert any beneficial function in the human? Conflicting evidence has been presented as to the development of carcinoma in the allergic population; however, in a review of over 1800 patients, it was felt that a lower proportion of people with malignant disease gave histories of allergic disorders than patients with other diseases.[10] It was also felt that there was a reduced risk of mortality from cancer among asthmatic patients.[10] Mechanisms, by which the IgE immune response may assist the host in response to neoplasia, have recently been reviewed.[11]

CELL-MEDIATED IMMUNITY (T-LYMPHOCYTE SYSTEM, DELAYED HYPERSENSITIVITY)

The transfer of cell-mediated immunity, unlike humoral immunity, requires the transfer of cells from one individual to another. The tuberculin reaction is a classic example of the cell-mediated immune response, although cell-mediated immunity is involved in a wide variety of immunologic events. These events include the delayed cutaneous hypersensitivity reaction, homograft rejections, responses to cancer, certain types of autoimmunity, as well as responses against some bacteria, viruses, fungi, and parasites.

There are at least two cell types participating in cell-mediated immunity. These cells include sensitized T-lymphocytes and macrophages. As in humoral immunity, the macrophage phagocytizes, processes, and presents antigens to the appropriate lymphocytes, thereby initiating an immune response. In cell-mediated immunity, however, the sensitized T-lymphocyte can alter several functions of the macrophage by releasing mediators. These macrophage-specific mediators constitute part of a larger group of mediators (lymphokines), which are released by T-lymphocytes after contact with antigen.

Lymphokines regulate the activity of the various cells involved in a cell-mediated immune response. The individual cellular activities which are mediated by lymphokines are collectively referred to as a cell-mediated immune response. Many lymphokines have been isolated and their functions characterized, although there are undoubtedly lymphokines which have yet to be isolated and characterized. Each lymphokine mediates a specific function for which it is named. The major lymphokines and the functions attributed to them include:

Chemotactic factor (Chemotaxin): This factor causes the active migration of mononuclear phagocytes to the region of the lymphocyte releasing the factor. It calls phagocytes to the area of insult.

Migration inhibition factors: These factors inhibit the migration of specific cell types. Two such factors are macrophage inhibition factor (MIF) and leukocyte inhibition factor (LIF). The factors prevent immune reactive cells from leaving the vicinity of the antigen.

Macrophage activation factor (MAF): Macrophages in the area of the sensitized T-lymphocyte are induced into a state of hyperphagocytosis. The resultant phagocytosis is nonspecific and some normal tissue is also destroyed.

Blastogenic factor (Blastogen): This lymphokine causes nonsensitized lymphocytes to enter blast cell transformation and mitotic proliferation.

Cytoxin: This factor has a nonspecific cytotoxic effect on viable cells. Its function is to kill viable antigens.

The combined effects of these lymphokines result in the recruitment of phagocytic cells to the vicinity of the antigen, the inhibition of migration of immunoreactive cells from the area of the antigen, the induction of hyperphagocytosis, the proliferation and activation of nonsensitized T-lymphocytes, and the death of many viable antigens. This cell-mediated immune system has the ability to destroy individual tumor cells. Manipulations of this system may become an important addition in the future therapy of carcinoma of the head and neck, combined with conventional therapy to decrease tumor load.

Presently, however, it appears that the study of cell-mediated immunity will be of more value in determining prognosis and in the early diagnosis of recurrences, rather than in the actual treatment of such lesions.

Several techniques, which can detect and quantify immune responses to tumor antigens, have been adapted to head and neck carcinoma.[12] It is hoped that these and other immunologic techniques will enable the physicians to detect the presence of tumor before it becomes clinically apparent.

By investigating the immunologic competence of patients with carcinoma of the head and neck, it may become possible to determine prognosis more accurately. Immune competence is evaluated by studying the patient's responses to a battery of immunologic tests. These tests include skin testing with common recall antigens (e.g., *Candida*, mumps, etc.), sensitization to the neoantigen dinitrochlorobenzene (DNCB)[13,14] and quantitation of T- and B- lymphocytes.[14-16]

INTERACTIONS BETWEEN TWO IMMUNE SYSTEMS

Although the classic division of the immune system has been presented, evidence is accumulating that these systems do frequently interact. Although the B-lymphocyte is indeed the producer of antibody, one subpopulation of T-lymphocytes (suppressor cells) hinders antibody production whereas another subpopulation of T-lymphocytes (helper cells) augments antibody production. One of the byproducts of complement fixation is a powerful chemotactic agent. Although not a lymphokine, this product of humoral immunity serves the same function as the lymphokine chemotaxin.

Another interaction between the two divisions is the conversion of null lymphocytes (neither B-lymphocytes nor T-lymphocytes) to killer cells (K-cells) by antibody. The antigenic specificity of the antibody is conferred upon the null lymphocyte during its transformation into a K-cell. These cells exhibit many characteristics of stimulated T-lymphocytes and are believed to be the predominant lymphoid cell type involved in tumor rejection.

Finally, humoral factors in some instances appear to prevent sensitized T-lymphocytes from destroying carcinoma.

CONCLUSIONS

As physicians we are aware of the intimate working relationship between the neurosurgeon and the neurologist and the abdominal surgeon and the gastroenterologist. Although we in otolaryngology work closely with specialists in various fields, we do not have the luxury of an established medical subspecialty dealing exclusively with medical aspects of otology, rhinology, and/or laryngology. We, therefore, must assume the leadership in bringing our interesting medical problems to the attention of our medical colleagues and working closely with them, in the clinic and in the laboratory, for the benefit of our patients.

Advances in the field of immunobiology have clinical relevance to our specialty and deserve our attention. Gordon[17] has written a short paperback containing clear concise definitions of many immunologic terms and concepts. Good and Fisher's[18] text contains outstanding diagrams and more detailed discussion. These works complement each other and should further demonstrate that the confusing terminology of immunobiology can be mastered without much difficulty.

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X-RAY OF THE MONTH

SPHENOID SINUS MUCOCELE SIMULATING A MALIGNANCY

RICHARD A. CHOLE, MD, PhD

SACRAMENTO, CALIFORNIA

CLINICAL HISTORY

The patient, a 64-year-old Caucasian male, noticed some obstruction in the right side of his nose for two months. During this time, he gradually developed periorbital pain and swelling and sought consultation with an otolaryngologist. On examination at that time, a right nasal mass was found, but a biopsy showed no tumor. His symptoms, however, progressed: six weeks prior to admission he developed reduced vision in his right eye. He was hospitalized by a neurosurgeon because of his progressive loss of vision. At that time, he had dysosmia and a right VI nerve paresis. Sinus x-rays were performed, and a lesion was seen in the sphenoid sinus with bony erosion (Fig. 1A). He then was referred to the Sacramento Medical Center where a necrotic mass was seen in the posterior nasal space. Tomograms of the paranasal sinuses showed extensive bone loss of the sphenoid sinus with almost no visualization of the sella turcica. In addition, ethmoid and left maxillary clouding were seen. A carotid angiogram showed deviation of both internal carotid arteries laterally in their course through the cavernous sinus. Computerized axial tomography demonstrated a soft tissue density in the area of the sphenoid sinus, posterior ethmoid sinuses, posterior nasal cavity, and right orbital apex (Fig. 1B). Three days after admission, the patient was taken to the operating room, and, under general anesthesia, biopsies of the nasal mass were performed. A sphenoidotomy was then performed by the transnasal route, and a large sphenoid sinus mucocele was found and marsupialized. Biopsies of the intranasal mass showed an undifferentiated carcinoma.

DISCUSSION

This patient demonstrated clinical and radiographic signs of a malignant tumor of the sphenoid and ethmoid sinuses with involvement of the right orbital apex. These findings would lead one to the erroneous conclusion that the patient had an inoperable tumor.

In actual fact, the patient had a resectable malignancy involving the ethmoid sinuses and posterior nasal cavity with obstruction of the ostia of the sphenoid sinus resulting in an expanding sphenoid sinus mucocele. This case graphically demonstrates a pitfall in the radiological assessment of tumors of the paranasal sinuses: bone erosion and sinus opacification may be caused by infection or mucocele even in the presence of a neoplasm.

Alexander,[1] in a discussion of sphenoid sinus tumors, noted that the radiographic findings in the sphenoid sinus are nonspecific and that radiographic findings must be supported by biopsy. Cranial nerve involvement is not necessarily a sign of malignancy. Nugent et al,[2] in a review of 63 cases of sphenoid sinus mucocele, found that 65% had impaired vision, 30% had involvement of the III or VI cranial nerves, and 14% had anosmia.

Ketcham et al,[3] cautioned that even with appropriate tomographic x-rays, the determination of the extent of local invasion of an ethmoid malignancy is

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From the Department of Otorhinolaryngology, University of California, Davis, Sacramento Medical Center, Sacramento, California.

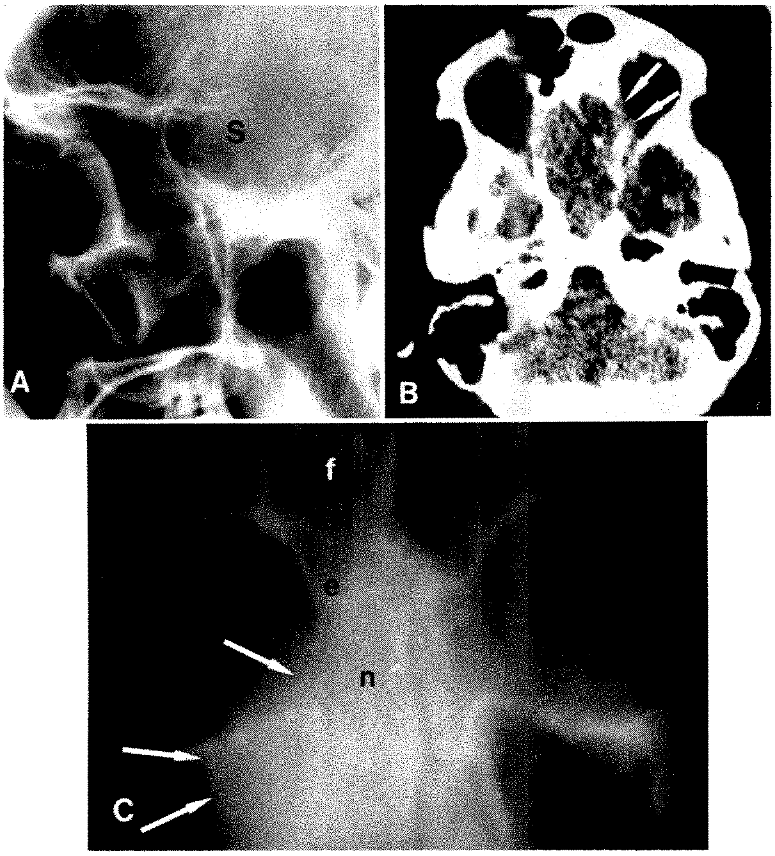

Fig. 1. A) Lateral view of the skull demonstrates an enlarged sphenoid sinus (S) with demineralization of the sella turcica. B) Computerized axial tomography demonstrates a soft tissue density in the area of the sphenoid and ethmoid sinus with probable extension into the right orbital apex (arrows). C) Thin section tomography in the AP plane shows opacification of the right ethmoid sinuses (e), the right frontal sinus (f), and the right nasal cavity (n). There appears to be erosion of the ethmoid septae and the supermedial wall of the maxillary antrum (arrows).

fraught with error. Potentially curative surgery may be withheld from a patient with a malignancy of the paranasal sinuses unless this pitfall is appreciated.

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3. Ketcham AS, Chretien PB, Van Buren JM, et al: The ethmoid sinuses: a reevaluation of surgical resection. Am J Surg 128:469-476, 1973

Reprints — Richard A. Chole, MD, Dept. of Otorhinolaryngology, University of California, Davis, Sacramento Medical Center, 4301 X Street, Room 208, Sacramento, CA 95817.

PAUL HENRY HOLINGER, MD

1906 - 1978

Paul H. Holinger, one of the most distinguished members of our profession, died on March 26, 1978.

Dr. Holinger's father, Jacques Holinger, was born and educated in Switzerland, coming to Chicago in 1892 where he was one of few who limited his practice to Otolaryngology; he had a special interest in the anatomy and pathology of the ear and was later appointed Associate Professor of Otolaryngology at the University of Illinois College of Medicine.

Because of his father's origins in Switzerland and an American mother who spoke fluent German, Paul grew up speaking both English and German, a skill which was often useful to him in later years. He attended the Parker School in Chicago in an atmosphere which encouraged individuality and independent thinking. His undergraduate years were spent at the University of Chicago where he earned a master of science degree through work done in gastric physiology with Andrew Ivy.

Following graduation from Northwestern University School of Medicine in 1933 and a residency at the University of Illinois, he became an assistant of the Jacksons in Philadelphia (1934-1935). On returning to Chicago he joined the Department of Otolaryngology at the University of Illinois and later, until becoming Emeritus in 1974, was Professor of Broncho-Esophagology at the Abraham Lincoln School of Medicine. He was also Professor of Otolaryngology at Rush-Presbyterian-St. Luke's Hospital Medical Center. He established the first bronchoscopic clinics in the Midwest at the Research and Educational Hospital of the University of Illinois, at Rush-Presbyterian-St. Luke's Hospital and at the Children's Memorial Hospital, where he brought the practice of pediatric laryngology and bronchoesophagology to an unsurpassed level of development. He was also a consultant at the United States Naval Hospital, Great Lakes, and the Armed Forces Institute of Pathology.

He was active in all of the national organizations related to our specialty and in recognition of his outstanding contributions in teaching and clinical research was elected President of the American Laryngological Association, the American Broncho-Esophagological Association, the American Society for Head and Neck Surgery, the American Society of Gastrointestinal Endoscopy and the American Council of Otolaryngology. He received the Casselberry, Newcomb and De Roaldes awards of the American Laryngological Association; he was Guest of Honor and was made an Honorary Fellow in 1977. He received the Chevalier Jackson Award of the American Broncho-Esophagological Association in 1962 and was made an Honorary Member in 1972 and Guest of Honor in 1974. He served as a director of the American Board of Otolaryngology (1963-1975) and was at various times governor, regent, and chairman of the Advisory Council for Oto-Rhino-Laryngology of the American College of Surgeons.

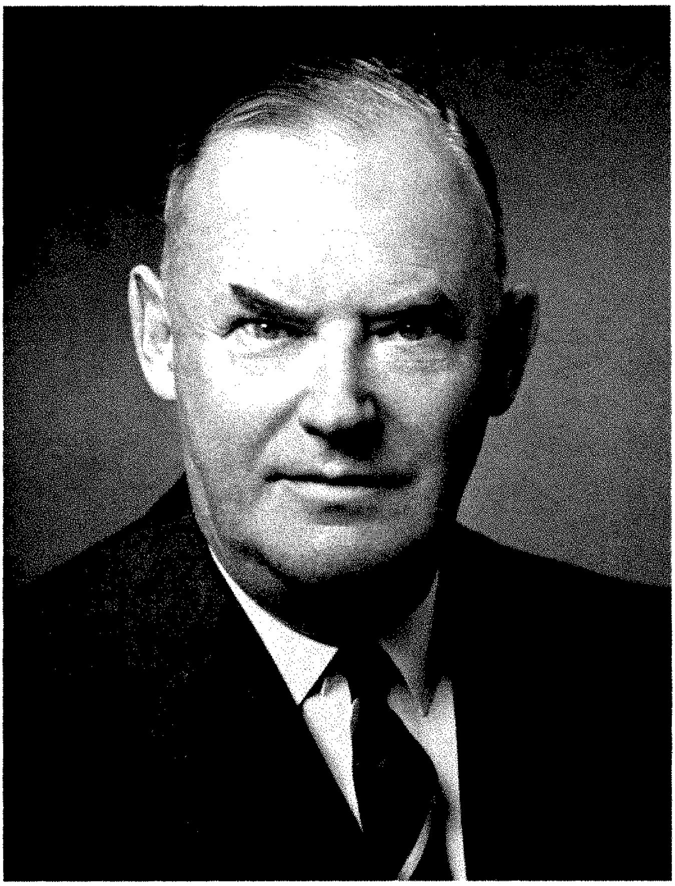
Dr. Holinger was also dedicated to international medicine and was awarded honorary membership in 27 foreign medical organizations. He was elected President of the International Broncho-Esophagological Society and the Pan American Society of Otolaryngology and Broncho-Esophagology. In 1957 he filled the demanding position of General Secretary for the VI International Congress of Otolaryngology. He was a member of the Collegium Otorhinolaryngologicum Amicitiae Sacrum.

His work in color still and motion picture endoscopic photography, begun more than 30 years ago, was recognized by five national and international awards. More than 300 of his scientific publications dealing with diseases of the air and food passages as well as new endoscopic instruments and photographic techniques have enriched our literature; the numerous special lectureships which he presented include the Semon Lecture.

Dr. Holinger and Julia Drake were married in 1939; they found great joy and satisfaction in family life with their four sons of whom the eldest, Lauren, became associated with his father in practice. Paul C. earned degrees in both theology and medicine and William and Richard became teachers.

Dr. Holinger was a man of strong personal convictions, forthright and honest in his association with his colleagues and yet endowed with an equanimity which was obvious to all with whom he associated. In his personal relationships he was always gracious, courteous and considerate. Despite having himself achieved the heights of professional attainment, he could always find time for those of lesser stature and he fully enjoyed his role as a preceptor and teacher. He was a physician in the finest tradition of the profession, dedicated, skilled, creative and compassionate. The heritage of our specialty has been immeasurably enriched by his accomplishments.

Charles M. Norris, MD



G. EDWARD TREMBLE, MD

1895-1977

Dr. Tremble was born in Montreal, Canada, on September 1, 1895. His early education was obtained at Montreal High School. He graduated, in Medicine, from McGill University in 1921. His postgraduate studies were carried out at the Montreal General and Royal Victoria Hospitals and in the otolaryngological clinics of Britain, Europe and the United States. During World War I he served in the Royal Navy with the rank of Sub-Lieutenant Surgeon. In 1930, he married Mary Hamilton, who died in 1967. In 1968, he married Mrs. Grace Paterson who, together with two daughters and one son from his previous marriage, survives him.

He held membership in British, European and American otolaryngological societies in addition to the Canadian Otolaryngological Society of which he was elected president in 1955. He made many contributions to the literature of his specialty. At his death he was an Emeritus Assistant Professor of Otolaryngology at McGill University.

In addition to being an able clinician, he was an artist, whose hobby contributed greatly to his own happiness and to that of his many friends. His out-going and amiable disposition resulted in his wide-spread popularity and large clinical practice.

On July 7, 1977, Ed Tremble, after finishing his dinner, complained that he was tired and laid down; an hour later, it was found that he had died in his sleep.

W. G. McNally, MD

Ann Otol 87:1978

REFLECTIONS OF AN OTOLARYNGOLOGIST

A SENSE OF AWE

WESLEY H. BRADLEY, MD
ALBANY, NEW YORK

A recent arrival on my desk initiated a train of thought which seemed worth sharing. The arrival was a beautifully prepared, and exceptionally expressive In Memoriam booklet from the family of the late Dr. Anderson C. Hilding. The purpose of this short piece is not primarily to eulogize Dr. Hilding, for this has been done far better by many others. Rather, it is to emphasize two points which emerge from the life of this very unique man.

The first point concerns his tenacity in continuing to be active in research as an individual investigator. This is not easy to do in today's research climate. I feel that this statement is eminently true, having just completed a significant period at the National Institutes of Health with the opportunity to see the biomedical research community from an overall perspective. However, Andy Hilding did not let this climate alter his life-long belief. He felt that there is no limitation to the physician's opportunity to observe, to record, to question, to develop hypotheses, and to put such hypotheses through objective and valid testing. It did not matter to him that the very great majority of such biochemical research is now done in highly organized units within academic medical centers and research institutions. To him the only requirements were a continuing inquisitiveness and desire to learn, plus a complete dedication to integrity as applied to the steps of the scientific method. Perhaps there are many who feel today that attempts at doing an investigative project are unrealistic unless one is part of a large center. Dr. Hilding's example would suggest that this is not necessarily so.

The second point concerns a very meaningful quotation in the booklet used to describe Dr. Hilding: "He never failed to be in awe of the Master Planner's works – the more he learned about the 'plans' the more was his awe." It is the word awe which caught my attention. Too often today we seem either too busy or we feel we are too sophisticated to let awe play any part in our lives. If we no longer can feel a sense of awe when new insights or dimensions are revealed to us, we have lost something most important both as scientists and as humanists. Perhaps we need to see again occasionally the excitement and awe in the face of a child who discovers a wonder of nature, such as a turtle or a beautiful piece of rock, and brings this new treasure to share with a parent.

My last visit with Dr. Hilding was at the conclusion of the Association for Research in Otolaryngology meeting in Dallas last fall. He was then 85 years old and he stayed until the program ended. When he saw me he came over and with obvious excitement told me some of the things he had heard and some of the new things he needed to learn more about. I feel sure that what I saw in his eyes that day was not only evidence of a never-ending inquisitiveness and desire to learn, but also a sense of awe.

BOOK REVIEWS

Essential Otolaryngology, Second Edition

Edited by *K. J. Lee.* Soft cover, black and white illustrations, indexed, sample tests, 592 pp, 1977. Medical Examination Publishing Co., Flushing, NY 11365. Price $18.00

The second edition of this book expands the scope and depth of the subjects covered in the first edition, as well as adding a much needed chapter on electrophysiology of hearing and balance. It provides an excellent outline for study in preparation for the Otolaryngology boards, a concise summary of each subject being discussed and a comprehensive bibliography, should the reader wish to explore a subject in greater depth.

The text is concise, well-written, and well-illustrated. The tables are well-organized and provide a wealth of condensed information.

Chapter 32, added to this second edition, consists of multiple choice questions. However, no answers are provided to encourage the reader to pursue the subject in greater depth.

This book is invaluable in helping the young otolaryngologist prepare for his board examination but should be of much assistance to the internist or general practitioner who wishes to become more familiar with various otolaryngologic conditions.

LAURENCE LEVINE, MD

Radiology of the Nose, Paranasal Sinuses and Nasopharynx

By *Gerald D. Dodd* and *Bao-Shan Jing.* Hard cover, black and white illustrations, referenced, indexed, 337 pp, 1977. The Williams and Wilkins Company, Baltimore. Price: $37.00

This volume represents Section 2 of the Golden's Diagnostic Radiology Series prepared under the general editorship of Dr. Laurence L. Robbins. Most older radiologists remember the original Golden's Radiology series as a two volume loose-leaf notebook of radiological information which evolved ultimately into an unwieldly three volume encyclopedia.

More recently the 22 sections of this series have been published as free-standing volumes, such as this text. The original notebook contained a 34-page treatise on both the paranasal sinuses and mastoids. The current volume has ten times as much space devoted to the sinuses and surrounding parts alone!

The experience of the authors has been gained primarily at the M. D. Anderson Hospital and Tumor Institute, so that one might suspect that the text would be unbalanced toward the description of tumors. Such is not the case. Indeed, the format of each part of the nose, paranasal sinuses, and nasopharynx is nicely balanced as far as content. Each part contains a description of the pertinent gross anatomy, radiological examinations available, and technique as well as roentgen anatomy and interpretation of the examinations. Chapters on inflammatory and nonneoplastic disease, trauma, benign and malignant tumors are included in the part describing the nose.

Particularly well done chapters on roentgen technique, anatomy and interpretation are found in the paranasal sinus section. A chapter on syndromes involving the paranasal sinuses describes the clinical and roentgen findings in generalized diseases such as Gardner's syndrome, basal cell nevus syndrome, neurofibromatosis, mucoviscidosis, Louis-Bar syndrome, Wegener's and midline lethal granuloma. Only a few developmental abnormalities are listed and sinus variations are dismissed with only a few illustrations. To the reviewer, lack of more comprehensive description of anatomic variations represents a deficiency of the text.

Chapters on inflammatory disease and cysts are very well arranged and illustrated. The chapter on trauma nicely outlines and illustrates the major forms of maxillofacial injury. As one might expect, the chapters on benign and malignant paranasal sinus tumors are the strong points of this section. One chapter nicely demonstrates tumor-like diseases of the paranasal sinuses. This segment of the book is completed by a presentation of postirradiation and postoperative changes of the paranasal sinuses. Of particular interest is the authors' differential radiographic features of post-radiation necrosis and postirradiation sarcoma.

Chapters on anatomy, radiographic technique and roentgen anatomy of the nasopharynx introduce this topic. The chapters on inflammatory diseases and benign tumors are very short, the latter consisting only of a description of the juvenile angiofibroma (already included in the paranasal sinus segment) and chordoma. A very comprehensive review of the features of malignant nasopharynx tumors, their lack of radiologic specificity and routes of spread into surrounding structures is presented.

Overall, this is an excellent book. Illustrations are first-rate and carefully chosen to clearly define the entity being described. Comprehensive reference material is included for further study. This book should become a basic text for every radiologist's library and deserves widespread use by otolaryngologists concerned with paranasal sinus and nasopharyngeal disease.

KENNETH D. DOLAN, MD

ABSTRACTS FROM NATIONAL AND INTERNATIONAL JOURNALS

Continuous Pump-Tube Enteric Hyperalimentation

Dobbie RP, Hoffmeister JA: Surg Gynecol Obstet 143:273-276, 1976

The authors emphasize that the devastating catabolic effects of many disease states can be reversed by nutritional intervention. They acknowledge that intravenous hyperalimentation promotes anabolism and improves immunocompetence, but carries a significant risk of catastrophic complications. They point out that these complications can be avoided in the patient with an intact gastrointestinal tract through the use of enteral hyperalimentation. They maintain that their technique is invariably successful, even in patients previously unable to tolerate bolus tube feedings.

They employ a lactose-free, isotonic feeding formula (Isocal®), administered as a continuous infusion. They maintain that elemental diets should not be routinely employed since they are hyperosmolar and expensive. They also maintain that if a small tube is placed in the proximal jejunum, large volumes of feeding can be administered without a period of adaptation and with almost no risk of reflux and aspiration.

J. Koufman

Dental Management of Patients Irradiated for Oral Cancer

Regezi JA, Courtney RM, Kerr DA: Cancer 38:994-1000, 1976

Regezi et al explain the need for consideration of oral health care in patients that are to receive radiation therapy. The authors show that teeth can be maintained provided a thorough diagnosis and health care program is instigated in patients prior to radiation therapy. The sequelae of radiation caries, peridontal disease and osteoradionecrosis can be controlled with proper treatment. Data from 130 patients for a period of one to ten years are evaluated exemplifying the type of care necessary to control these patients with the support of long-term data indicating the success of oral care programs. The oral cancer patient can be favorably rehabilitated.

W. LaVelle

Carcinoma of the Oral Cavity: Factors Affecting Treatment Failure at the Primary Site and Neck

Shah JP, Cendon RA, Farr HW, et al: Am J Surg 132:504-507, 1976

The authors have attempted to identify those patients at a higher risk of recurrent local and/or regional (neck) disease following initial treatment of epidermoid carcinoma of the oral cavity. Seven hundred and fifty-eight patients were studied with a ten-year follow-up available on all patients. Those patients with local and/or regional recurrences (334) were compared to the patients with controlled disease (370) in relation to several clinical and pathological parameters. (The remaining 54 patients developed distant metastases.) Females, in general, were found to do more poorly than males. The rate of recurrent disease also increased with advancing stage of disease and degree of clinical invasion, presence of tumor at the surgical margins, presence of extracapsular involvement of cervical lymph nodes, soft tissue involvement in the neck, and advancing number and level of nodes involved. The authors urge that the data presented be used in the selection of appropriate patients for multimodality therapy.

S. Baredes

Squamous Cell Carcinoma of the Oropharynx: Why We Fail

Jesse RH, Sugarbaker EV: Am J Surg 132:435-438, 1976

The treatment of oropharyngeal carcinoma in 384 patients was reviewed to explore reasons for treatment failure. Failure included 72 patients (19.5%) with recurrence at the primary site; 42 (11.3%) with recurrence in a neck node; 35 (9.5%) with distant metastases; 24 (6.5%) dead of unknown causes; 17 (4.5%) dead due to treatment. Thirteen patients were treated palliatively and were eliminated from the study.

Treatment included radiotherapy and surgery, singly or combined, and varied according to TNM classification factors peculiar to the patient and to treatment team experience. In general, T_1, T_2, T_3, N_0, N_1 and most T_4 lesions were treated with a single modality. Some T_3 and T_4 lesions received combined therapy.

Local recurrence was much more frequent in T_3 and T_4 lesions and significantly more frequent in patients with palpable neck nodes or with oropharyngeal lesions as opposed to faucial arch cancers.

Failure of neck treatment was greatest in N_2b and N_3 class necks with only one fourth of these patients in the nonfailure group. Of the patients with one or no neck nodes, 89% were in the nonfailure group. Of patients with distant metastases 86% had positive nodes in the neck at the time of initial treatment.

The authors point out that 54 of the 144 patients (37%) surviving five years developed a *second primary* cancer in either the oropharynx, hypopharynx, esophagus, or lung.

It was suggested that T_3 lesions need a systematic combined approach; patients with class N_2 and N_3 neck nodes need whole neck radiation followed by neck dissection for all patients with pretreatment clinically positive nodes; and patients with Stage IV disease (American Joint Commission on Staging Systems) need treatment modalities beyond surgery and radiation therapy (i.e., chemotherapy or immunotherapy).

W. McMillan

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For further information contact: Janusz Bardach, MD, Division of Plastic and Reconstructive Surgery of the Head and Neck, Department of Otolaryngology and Maxillofacial Surgery, University of Iowa Hospitals, Iowa City, IA 52242.

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Section Meeting
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October 23-24, 1978

PROGRAM

October 23, 1978 (Open Session).

Topics: Croup and Epiglottitis, Gerald B. Healy, MD
Recent Advances in Otitis Media, Charles Bluestone, MD
Assessment of Hearing in Early Life, Robert Ruben, MD

October 24, 1978 (Closed Session for Section Members)

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2. Head and Neck Tumors
3. Learning and Behavioral Dysfunction in the School Age Child

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For information contact: Gerald B. Healy, MD, 300 Longwood Ave., Boston, MA 02115.

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2. To provide instructional courses in anatomy of the posterior cranial fossa and temporal bone as well as basic audiology and vestibular testing.

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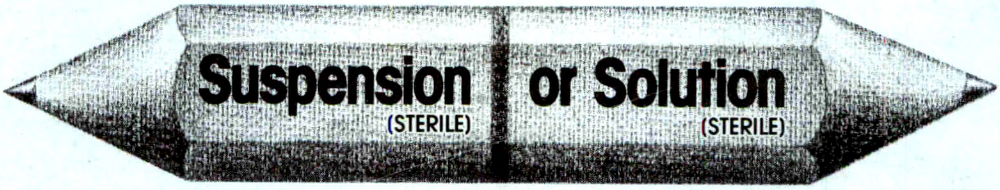

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ANIMAL MODEL FOR THE 4-kHz TONAL DIP

William W. Clark, PhD

Barbara A. Bohne, PhD

St. Louis, Missouri

In humans, noise exposures produce permanent hearing losses which usually begin at 4 kHz. In chinchillas, a similar pattern of hearing loss was observed following exposure for 9 or 18 days to an octave band of noise with a center frequency of 0.5 kHz. Histopathological observations of cellular degeneration showed that this exposure produced different types of damage in the basal and apical turns of the cochlea. Behavioral measures of auditory function showed that damage in the basal turn was associated with permanent threshold shifts for one to several of the high frequencies. However, moderate losses of outer hair cells commonly appeared in the apical turn without permanent threshold shifts for low-frequency tones. These findings indicate that the pure-tone audiogram may not accurately reflect the condition of the organ of Corti after noise exposure.

It has long been observed that humans exposed to occupational or recreational noise first develop hearing losses for the high-frequency tones, regardless of the frequency content of the exposure.[1-5] The term "4-kHz notch" or "4-kHz tonal dip" has been coined to describe the hearing loss of a typical noise-exposed person, although the notch has been found to occur anywhere from 3 to 6 kHz.[5] As a person's exposure to noise continues, permanent hearing losses begin to appear at frequencies above and below 4 kHz. Generally, only after long histories of noise exposure do hearing losses occur in the frequencies considered most important for speech discrimination.

Bohne and associates[6,7] studied the ears of chinchillas which were exposed for two or more days to an octave band of noise (OBN) with a center frequency of 0.5 kHz at 95 or 103 dB sound pressure level (SPL). In addition to moderate losses of outer hair cells (OHC) in the apex, they found that in the basal turn, part of the organ of Corti had completely degenerated. The degeneration encompassed all sensory cells and supporting cells, as well as the corresponding afferent nerve fibers. Because the basal-turn lesions occurred near the region presumed to correspond to 4 kHz, it was hypothesized that animals exposed to low-frequency noise would first develop permanent threshold shifts (PTS) for high-frequency tones. The present study was designed to test this hypothesis by observing behavioral threshold shifts and corresponding histopathology in both the low- and high-frequency regions in animals exposed to low-frequency noise.

METHODS AND MATERIALS

Subjects. Twelve 1- to 2-year-old chinchillas were used in this study. Six animals were used for anatomical studies only, whereas the other six animals were used for both behavioral and anatomical studies. All animals were housed in sound-shielded quarters prior to and following their noise exposures. The animals for the behavioral studies were made monaural by surgically destroying the left cochlea.[8] There were no postoperative complications and antibiotic treatment was not employed.

Audiometric Testing Apparatus. Audiometric testing was carried out inside a double-walled sound-shielded booth (IAC Model 1202). A 1.27 cm hardware cloth cage, similar to one previously described,[9] was suspended in the booth 0.3 m from the floor and 0.6 m from a speaker system (Altec 605A) which was mounted on a pedestal and enclosed in a large, fiberglass-lined 1.91 cm pressboard enclosure. The pedestal raised the speaker to the same height as the cage. The speaker and test cage were placed diagonally across the booth from

---

From the Central Institute for the Deaf and the Department of Otolaryngology, Washington University School of Medicine, St. Louis, Missouri.

each other, and the walls of the booth behind the cage were lined with 5.08 cm fiberglass insulation. A key/feeder chute and pellet dispenser (Gerbrands) were mounted at one end of the test cage.

Pure-tone test stimuli were generated by an oscillator (Hewlett-Packard 4204A) and monitored by a frequency counter (Hewlett-Packard 5321A). Stimuli were presented to an amplifier (Crown D-150A) via an electronic switch (Grason-Stadler 829D, 50 msec rise/fall time) and a recording attenuator (Grason-Stadler E5135C), with gearing arranged to provide a 4-dB step size. The amplified signal was presented to the speaker system and monitored by an AC voltmeter (Hewlett-Packard 400F). The attenuator, electronic switch, pellet dispenser, and the recording of responses were controlled by a modified solid-state logic system (Iconix).

Signals were calibrated and checked periodically with a condenser microphone (Bruel and Kjaer 4133) and an audio-frequency spectrometer (Bruel and Kjaer 2112). The microphone was positioned in the cage at the approximate location of the animal's right ear when it was pressing the response key.

Noise Exposure Facility. The reverberant room used for noise exposure has been described previously.[10] Briefly, a noise generator and an octave-band filter (Allison) were used to produce an OBN with a center frequency of 0.5 kHz. The signal was amplified by a 275-watt amplifier (Altec) before being presented to an Altec speaker system (N800 crossover network and a 38.1 cm woofer). During their exposures, the animals were housed in a cage divided into four compartments which was located in the center of the reverberant room. The SPL in the compartments were determined with a sound level meter (Bruel and Kjaer 2203) and condenser microphone (4132). The spectral analysis of the noise was determined in one-third octave bands with the condenser microphone, the audio-frequency spectrometer, a multifilter and multichannel RMS detector (General Radio 1925 and 1926).

Behavioral Training. Animals were trained to report the presence of pure-tone test stimuli by releasing a response key.[9] Initially, depressing the key immediately produced a clearly-audible tone (1-4 kHz, 60-70 dB SPL), that remained on until a key release occurred. Releases turned off the tone and delivered a 45-mg pellet (Noyes) to the feeder chute mounted on the response key. Gradually the interval between the key press and the onset of the tone was delayed; releases before the tone onset were not reinforced. The trial duration was shortened to two seconds and stimulus-free blank trials were introduced once the animal was reliably releasing the key after the onset of the tone. The correct response to a blank trial was to continue to hold the key through the termination of the two-second trial (correct rejection), and was followed by delivery of a food pellet. Incorrect responses (premature releases or false alarms) produced a three-second time out from the experiment. Spontaneous responding was monitored via the false alarm rate, and was restricted to 5-15% by varying the a priori odds of tone versus blank trials during training. After the animal was reliably reporting stimuli and holding through blank trials, threshold testing was begun.

Threshold Testing. Pure-tone thresholds at a number of test frequencies were determined by means of the tracking procedure.[9] Each release of the key during the stimulus ("hit") decreased the sound pressure of the stimulus by 4 dB before the next trial; similarly, each failure to release the key during the two-second tone trial ("miss") produced a 4-dB increase in stimulus level. Behavior during blank trials did not affect the level at which the stimuli were presented. Testing continued at a given frequency until eight transitions (crossings from "hit" to "miss" or vice versa) had occurred. Threshold was defined as the mean of the levels of the last six transitions. Generally, five to seven thresholds could be obtained during each daily, one-hour test session for each chinchilla. During the session a chinchilla consumed approximately 250 pellets and was given enough extra ration after the session to insure that its weight was maintained above 80% of its ad libitum value.

At the beginning of the study, six test frequencies were selected, baseline data obtained and then thresholds for those tones were measured daily before, during, and after noise exposure. After four behaviorally-trained animals were tested with this protocol, it was noted that the position of anatomical damage in the high-frequency region was not constant. Therefore, the testing protocol was modified so that thresholds were obtained at quarter-octaves from 0.5 to 11.3 kHz.* Since an average of only six frequencies could be tested per day in a given animal, approximately three days were needed to obtain a complete audiogram. Preexposure baselines were calculated as the mean of at least five thresholds obtained on separate days. Standard deviations of the baseline thresholds varied between animals and between test frequencies, but averaged about 3.5 dB. Postexposure audiograms were obtained by averaging thresholds from day 10 to day 30 of recovery.

Noise Exposure. All animals were exposed to a 0.5-kHz OBN at 95 dB SPL. Spectral characteristics of the noise are shown in Figure 1. The level of the noise decreased 26 and 28 dB/octave below and above the exposure band, respectively. One-third octave-band levels in the 4-kHz region were -40 dB with respect to the level at 0.5 kHz. The levels in individual compartments fell within a range of ±1 dB but that in the compartment with the shortest reflection path to the source tended to be 0.5-1.0 dB above those in the other compartments.

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*0.5, 0.6, 0.715, 0.85, 1.0, 1.2, 1.4, 1.68, 2.0, 2.37, 2.8, 3.35, 4.0, 4.8, 5.7, 6.7, 8.0, 9.6, and 11.3 kHz.

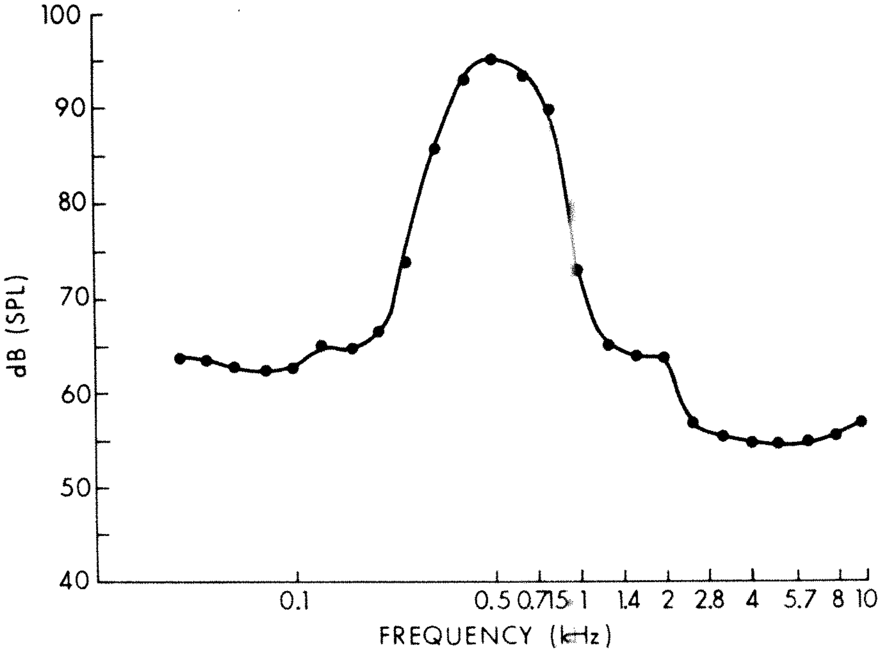

Fig. 1. Acoustic measure of SPL in one-third-octave bands for 0.5-kHz octave-band noise at 95 dB SPL.

The duration of the exposure was 9 days for half of the animals and 18 days for the rest. The trained animals were removed from the noise approximately one hour per day for testing; the untrained animals were exposed continuously. The exposure cage was rotated one-fourth turn daily in an attempt to insure equivalent exposure to all animals.

Histological Technique. Some of those animals which were used solely for anatomical study were sacrificed within an hour following termination of the exposure. The rest of the animals, including the behaviorally-trained ones, were sacrificed after a one-month recovery period.

In the exposed animals, no changes in thresholds were observed between day 10 and day 30 of recovery. Earlier studies had shown that cell degeneration and scar formation in the organ of Corti are complete by 30 days following exposure to moderate levels of noise.[6,11] Thus, it is presumed that the one-month recovery period was sufficient to allow the hearing losses and inner ear damage to stabilize in the behavioral animals used in the present study.

All specimens were prepared for histological study in the same fashion. Following in vivo fixation with 1% osmium tetroxide in Dalton's buffer, the intact cochleae were dehydrated and embedded in araldite. Once the plastic had polymerized, the cochleae were dissected so that flat preparations of the entire cochlear duct could be made. Full details of this technique have been published previously.[12]

The extent and location of sensory cell loss and organ of Corti and strial degeneration were determined in all specimens. Damage was graphically expressed as percentage missing inner (IHC) and OHC as a function of percentage distance from the cochlear apex.

RESULTS

In order to summarize the histological findings and to simplify comparison between the 9- and 18-day ears, the following strategies were adopted:

1. The OBN centered at 0.5 kHz covered the frequencies from 0.355 to 0.710 kHz at its 3 dB down points. Its approximate position was located on the basilar membrane using a frequency-place map of the chinchilla cochlea.[13] It corresponded to the region from 16-30% of the distance from the apical end of the organ of Corti. Since damage in this region generally consisted of scattered loss of OHC only, the average percent missing OHC was calculated for this area.

TABLE 1. SUMMARY OF ANATOMICAL DAMAGE IN EARS EXPOSED FOR NINE DAYS TO 0.5-kHz OBN AT 95 dB SPL

Specimen No.	*Length (mm)*	*% Missing OHC Low-Freq. Region*	*Size HFL (mm)*	*Location HFL (%)**	*Size Strial Atrophy (mm)*	*Location Strial Atrophy (%)**
Acute						
204 R	18.72	14.6	.14	76.8-77.5	1.14	59.5-65.6
204 L	18.48	18.2	—	—	1.13	58.8-64.9
248 R	19.26	25.9	.10	58.7-59.2		
			.10	65.4-65.9	—	—
			.11	68.0-68.6		
248 L	19.25	29.9	.22	55.8-57.0	—	—
Long-term						
240 R†	18.28	5.8	.28	71.2-72.7	—	—
280 R (B)	18.16	18.8	—	—	—	—
281 R (B)	17.34	20.3	.14	59.4-60.2	—	—
			.28	74.6-76.3		
313 R (B)	18.14	20.9	—	—	—	—

OBN - Octave band of noise; SPL - Sound pressure level; OHC - Outer hair cells; HFL - High-frequency lesion.

Acute - Less than 1 hour of recovery; Long-term - 1 month of recovery.

* - Percent distance from cochlear apex.

† - 240 L had ossicular removal prior to exposure and therefore was not exposed at 95 dB SPL.

(B) - Behaviorally-trained subjects.

2. Damage was termed a "high-frequency lesion" if it was located in the basal half of the cochlea (50-100% of distance from apex) *and* if it exceeded 50% loss of OHC.

3. A lesion was termed a "wipeout" if all sensory and supporting cells had degenerated.

Nine-Day Exposure. Table 1 summarizes the histological findings in the ears exposed to noise for nine days. In the low-frequency region, OHC loss ranged from 5.8 to 29.9% and averaged 19.3%.* Five of the eight ears had one or more high-frequency lesions (HFL). The HFL ranged from 0.10 to 0.28 mm in extent and averaged 0.17 mm. These lesions were found to vary in position from 55.8 to 77.5% (i.e., approximately 2.37-6.7 kHz). No systematic relation was found between cochlear length and position of the HFL (Table 1). Two of the eight ears had a region of total strial atrophy which was located in the basal turn.**

The pre- and postexposure audiograms and cochleograms for the behaviorally-trained animals in this group are shown in Figures 2-7. All behavioral data are plotted as threshold shift in decibels from the animal's pre-exposure baseline. A threshold shift greater than 10 dB is considered significant.

The audiograms and cochleogram for chinchilla 280 are shown in Figures 2 and 3. Daily threshold measures were obtained at 0.5, 0.715, 1.0, 2.8, 4.0, and 5.7 kHz. Figure 2 shows that this animal had a relatively flat temporary hearing loss which averaged 22 dB in the low frequencies and 20 dB in the high frequencies. The animal's shifted thresholds remained stable throughout the exposure. This animal had no PTS at any frequency tested. Its cochleogram showed a broad loss of OHC in the low-frequency region which averaged 18.8%. Very little sensory cell loss occurred elsewhere in the ear (Fig. 3).

Chinchilla 281 was tested with the

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*Nonexposed chinchilla cochleae are missing an average of 39 outer hair cells in the organ of Corti. Cell loss never amounts to more than 1.5% in any one location.

**See references 6 and 7 for illustrative photomicrographs of 1) "wipe-out," 2) strial atrophy, 3) pattern of hair cell loss in low-frequency region and 4) pattern of damage in high-frequency region of organ of Corti.

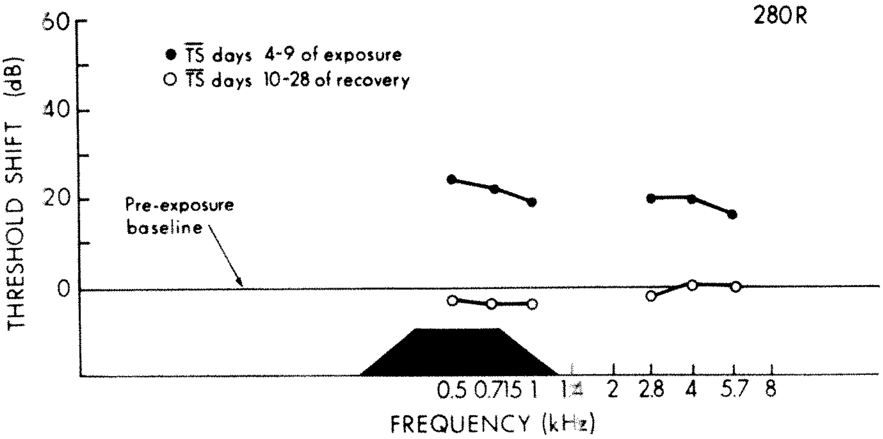

Fig. 2. Graph showing average threshold shift ($\overline{TS}$) and recovery for subject 280 following exposure to 0.5-kHz OBN at 95 dB SPL for nine days. The trapezoid indicates the range of frequencies present in the 0.5-kHz OBN.

same protocol as animal 280. It sustained temporary threshold shifts (TTS) which averaged 28 dB in both the low and high frequencies. The animal had no significant PTS at any frequency tested, although there may have been some indication of a permanent loss at 1 and 2.8 kHz (Fig. 4). The cochleogram for chinchilla 281 (Fig. 5) showed that OHC loss averaged 20.3% in the low-frequency region. In addition, the ear had two high-frequency lesions: a 0.14 mm lesion at 59% (approximately 2.4 kHz), and a 0.28 mm lesion at 76% (approximately 6.7 kHz).

Chinchilla 313 was tested at quarter-octave intervals prior to exposure and after recovery had been completed. During the exposure and the first few days of recovery, thresholds were measured daily at 0.715 and 2.8 to 8.0 kHz. Threshold shifts averaged over days 4-9 of exposure were 29 dB at 0.715 kHz and 38 dB for the high frequencies. No permanent hearing loss occurred below 1.4 kHz. This animal had a small,

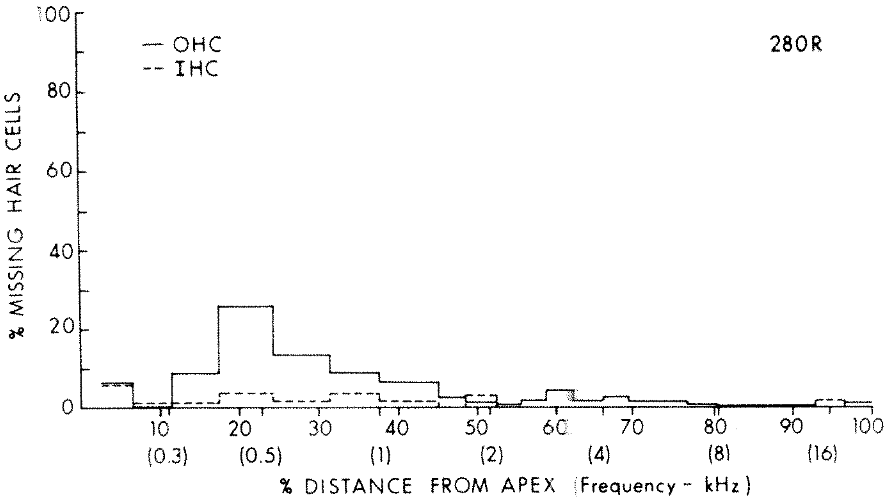

Fig. 3. Cochleogram for subject 280, depicting percentage missing sensory cells as a function of percent distance from the apex of the cochlea.

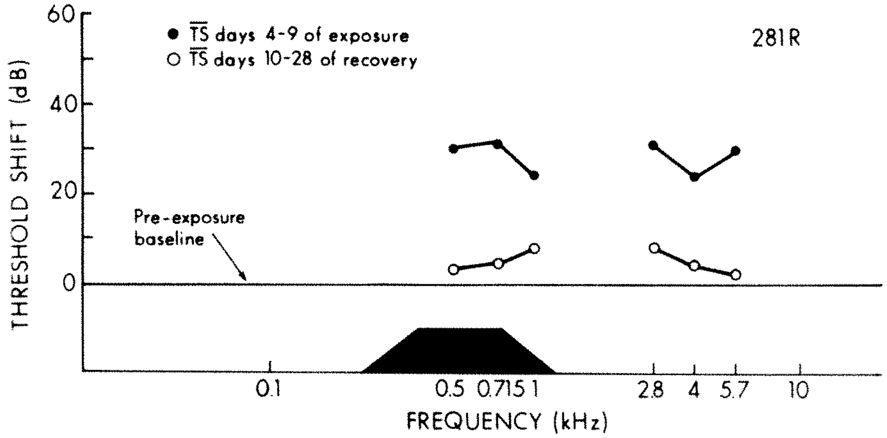

Fig. 4. Graph showing average threshold shift and recovery for subject 281 following exposure to 0.5-kHz OBN at 95 dB SPL for nine days.

nearly flat PTS from 1.68 to 11.3 kHz with a peak loss of 21 dB at 3.35 kHz (Fig. 6). The cochleogram for animal 313 showed an average loss of OHC of 20.9% in the low-frequency region, a small concentrated loss of IHC and OHC at 36% (approximately 0.85 kHz) and very little sensory cell loss throughout the rest of the cochlea (Fig. 7).

Eighteen-Day Exposure. Table 2 summarizes the histological findings in the ears exposed to noise for 18 days. In the low-frequency region, OHC loss ranged from 6.7 to 20.3% and averaged 13.9%. All nine ears in this group had at least one high-frequency lesion. The extent of the HFL ranged from 0.08 to 0.33 mm and averaged 0.20 mm. These lesions were found to vary in position from 49.3 to 77.6% (1.68 to 6.7 kHz). Again no systematic relation was found between cochlear length and position of high-frequency lesion (Table 2). Three of the nine ears had a region of total strial atrophy which was located in the basal turn.

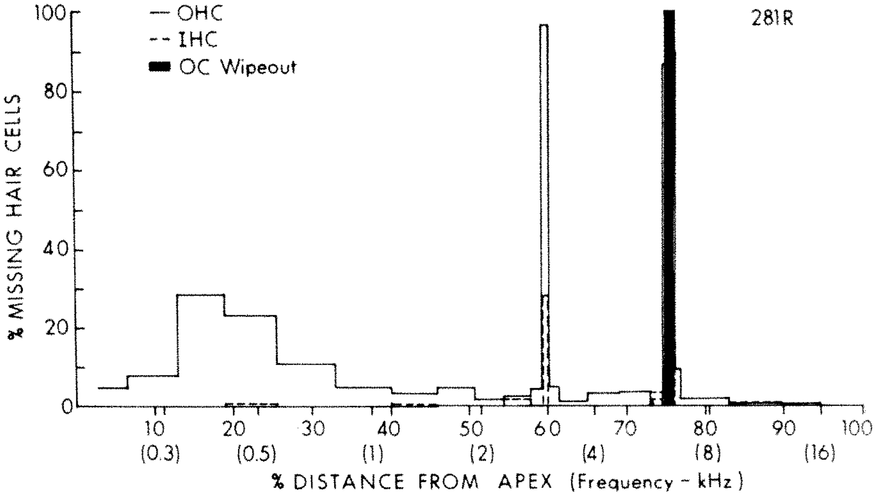

Fig. 5. Cochleogram for subject 281, depicting percentage missing sensory cells as a function of percent distance from the apex of the cochlea. Solid bar indicates region in which entire organ of Corti (OC) has degenerated.

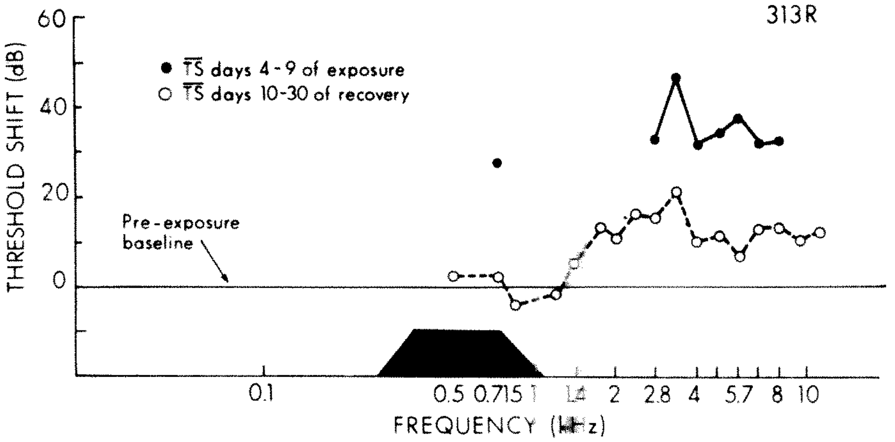

Fig. 6. Graph showing average threshold shift and recovery for subject 313 following exposure to 0.5-kHz OBN at 95 dB SPL for nine days.

The pre- and postexposure audiograms for the behaviorally-trained animals in this group are shown in Figures 8-13. Chinchilla 285 was tested daily at 0.5, 0.715, 4.0, 4.8, 5.7, 6.7, and 8 kHz. Its threshold shifts at all frequencies averaged 40-50 dB for the first nine days of exposure. Over the next nine days the thresholds did not change significantly from these initial levels. This animal had a PTS of 16 dB at 4.8 kHz and 15 dB at 5.7 kHz. The thresholds at the other test frequencies returned to pre-exposure values (Fig. 8). The cochleogram for animal 285 showed an average loss of OHC in the low-frequency region of 19.5%. A 0.12 mm high-frequency lesion was located near the 2-kHz place. Only small losses of OHC were found in the 4-kHz region (Fig. 9).

Chinchilla 286 was tested with the same protocol as 285. It had a 40-50 dB threshold shift which remained nearly constant for the entire exposure period. This animal had no PTS for the low frequencies. It had a 30 dB PTS

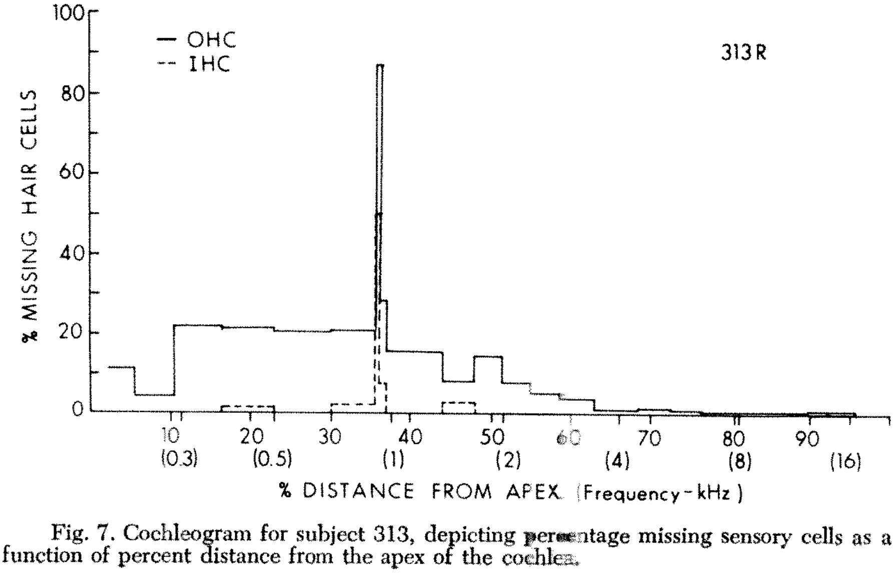

Fig. 7. Cochleogram for subject 313, depicting percentage missing sensory cells as a function of percent distance from the apex of the cochlea.

TABLE 2. SUMMARY OF ANATOMICAL DAMAGE IN EARS EXPOSED FOR 18 DAYS TO 0.5-kHz OBN AT 95 dB SPL

Specimen No.	*Length (mm)*	*$\overline{\%}$ Missing OHC Low-Freq. Region*	*Size HFL (mm)*	*Location HFL (%)**	*Size Strial Atrophy (mm)*	*Location Strial Atrophy (%)**
Acute						
276 R	19.59	6.7	.10	57.4-57.9	—	—
276 L	19.68	10.3	.24	49.7-50.9	—	—
			.14	62.2-62.9		
283 R	18.35	20.3	.23	62.1-63.4	—	—
283 L	18.16	15.2	.23	59.2-60.5	—	—
			.08	68.2-68.6		
Long-term						
284 R	18.74	12.4	.31	52.9-54.5	2.23	74.8-86.6
284 L	18.44	13.2	.33	56.9-58.7	2.58	71.5-85.4
285 R (B)	18.85	19.5	.12	49.3-50.3	—	—
286 R (B)	18.93	8.7	.21	76.5-77.6	1.16	64.8-70.9
329 R (B)	19.30	19.0	.11	53.8-54.4	—	—
			.31	71.3-72.9		

at 4 kHz that declined nearly linearly with log frequency to reach 0 dB at 6.7 kHz (Fig. 10). The cochleogram for chinchilla 286 showed an average loss of OHC in the low-frequency region of 8.7%. There was a 0.21 mm high-frequency lesion at approximately 6.7 kHz and a 1.16 mm region of strial atrophy which extended from approximately 2.8 to 5.7 kHz (Fig. 11).

Chinchilla 329 was tested at quarter-octave intervals prior to exposure and after complete recovery. Threshold shift during exposure reached a maximum of 50 dB at 2 kHz. The hearing losses remained stable throughout the 18 days of exposure. This animal had a PTS of 21 dB at 0.715 kHz. It also had a broad hearing loss which extended from 1.68 to 5.7 kHz, with peaks of 23 dB at 2.37 kHz and 26 dB at 4 kHz (Fig. 12). In this animal, OHC loss in the low-frequency region averaged 19%. There was a 0.11 mm high-frequency lesion at 2.37 kHz and a 0.20 mm lesion at approximately 5 kHz (Fig. 13).

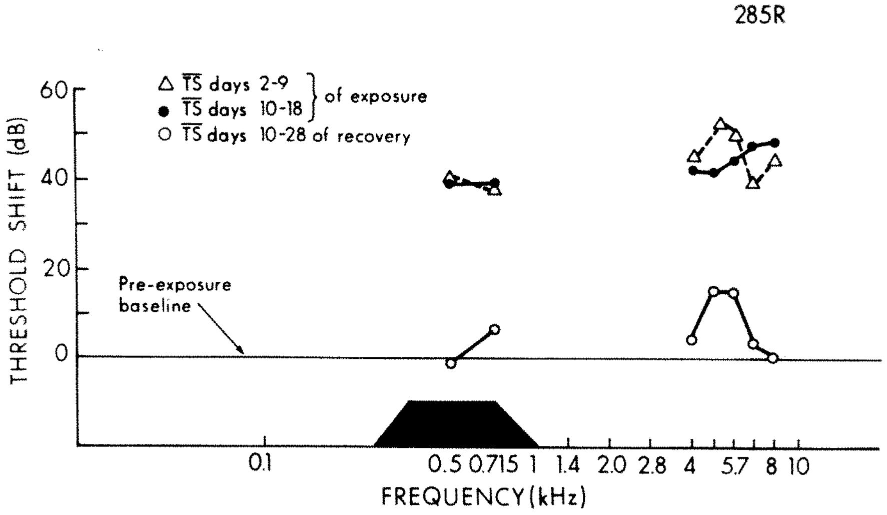

Fig. 8. Graph showing average threshold shift and recovery for subject 285 following exposure to 0.5-kHz OBN at 95 dB SPL for 18 days.

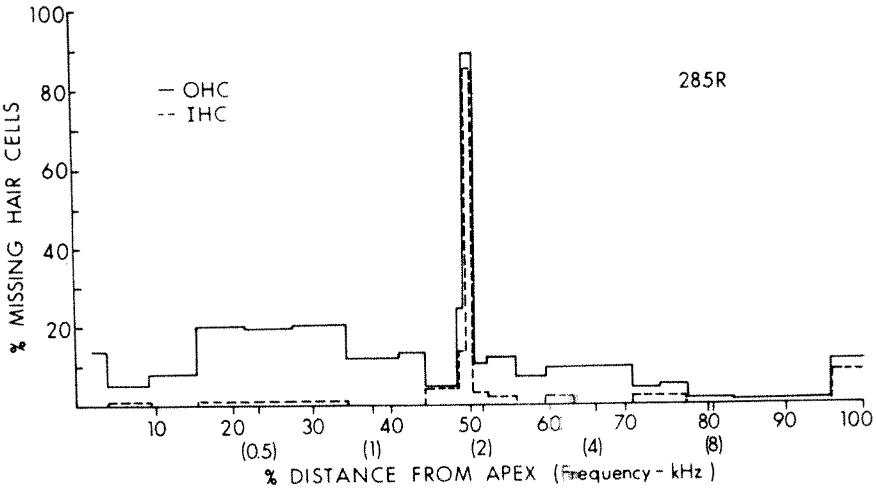

Fig. 9. Cochleogram for subject 285, depicting percentage missing sensory cells as a function of percent distance from the apex of the cochlea.

DISCUSSION

Asymptotic Threshold Shift (ATS). Carder and Miller[10,14] found that when chinchillas were exposed to moderately-intense noise, their hearing thresholds continued to increase for 18-24 hours. The thresholds then stabilized or reached asymptotic levels such that continued exposure for up to 21 days did not result in any additional loss of sensitivity. Similar findings have been reported in humans by Mills et al[15] and Melnick.[16,17] Based on this finding, it has been postulated that the presence of an asymptote might indicate that the ear is in a state of equilibrium[18] and that the level of the shift at asymptote might be predictive of the PTS produced by the same noise after a number of years of exposure.[19,20]

Previously it was shown that sensory cell loss increased as the duration of the exposure was lengthened from two to nine days.[7] In the present study, extending the duration of exposure from 9 to 18 days increased the likelihood of

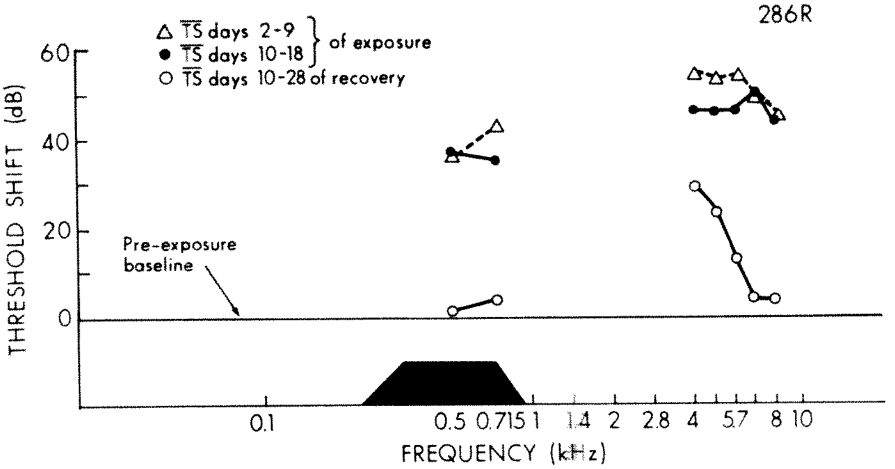

Fig. 10. Graph showing average threshold shift and recovery for subject 286 following exposure to 0.5-kHz OBN at 95 dB SPL for 18 days.

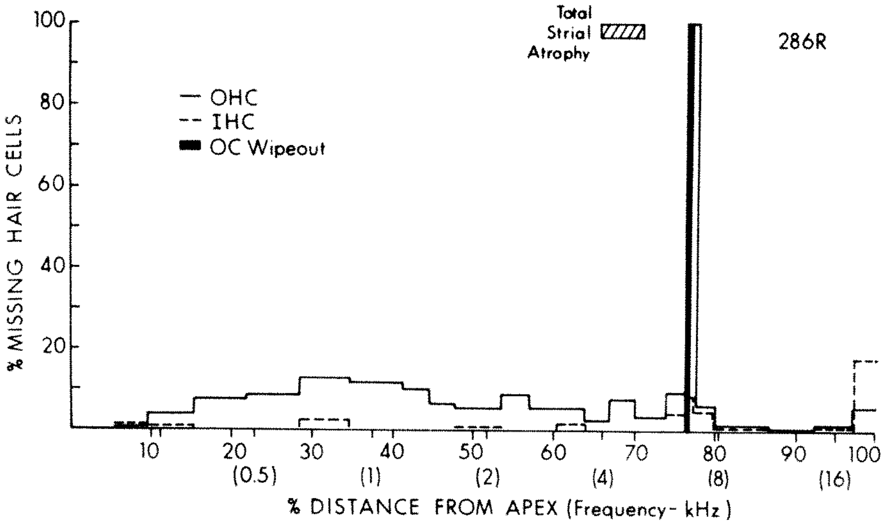

Fig. 11. Cochleogram for subject 286, depicting percentage missing sensory cells as a function of percent distance from the apex of the cochlea. Hatched bar indicates region in which stria vascularis has entirely degenerated.

damage in the high-frequency region of the cochlea and also tended to increase its severity. Damage in the low-frequency region remained relatively constant between 9 and 18 days.

The behaviorally-trained animals in the 18-day group showed no increase in their shifted thresholds from day 1 to day 18 of exposure. Although this finding tends to indicate that the ear is in a state of equilibrium, the anatomical data suggest otherwise. Therefore, it is predicted that as the duration of exposure is extended, the thresholds will eventually increase, once cellular damage exceeds a "critical level." Exactly what the "critical level" is remains to be determined. This prediction matches the hypothetical growth curve for PTS of Mills which was labelled "non-asymptotic PTS."[20] Mills stated that this type of growth would imply that the

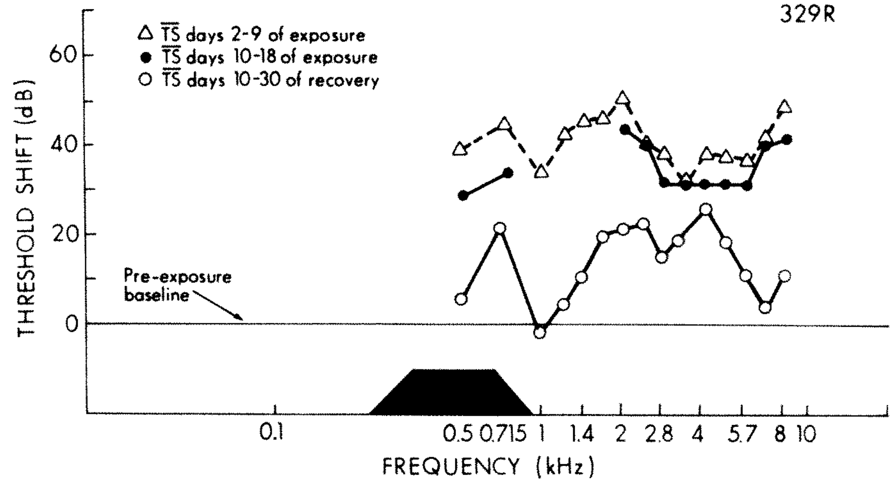

Fig. 12. Graph showing average threshold shift and recovery for subject 329 following exposure to 0.5-kHz OBN at 95 dB SPL for 18 days.

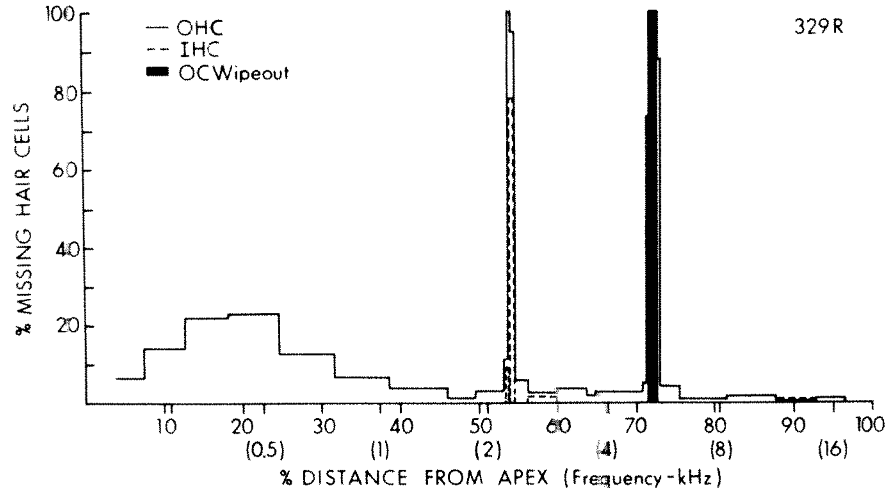

Fig. 13. Cochleogram for subject 329, depicting percentage missing sensory cells as a function of percent distance from the apex of the cochlea.

inner ear is in a state of "disintegration" either at selected regions or perhaps along its entire length. Clearly, exposures of longer durations are needed to test this hypothesis.

Temporary Versus Permanent Hearing Loss. As stated above, the level of the threshold shift during exposure remained constant while cell loss increased. However, PTS was found to increase with increasing duration of exposure. In the 9-day-exposure group, only one of the three animals had a PTS whereas all of the animals in the 18-day group had PTS. The temporary component of the threshold shift which was present *during* the exposure masked the slowly increasing PTS. In order to determine the growth pattern of PTS, it is necessary to expose groups of trained animals to the same noise for different durations and then to compare their postexposure audiograms. The data reported here are the beginning of such a study.

Permanent hearing losses occurred for the high frequencies even though most of the energy in the exposure was in the low frequencies. This finding clearly suggests that evaluation of the effects of a particular noise exposure should include the testing of frequencies across the entire hearing range rather than restricting testing to the frequencies near that of the exposure.

Relation Between Permanent Threshold Shift and Cell Loss. For a number of years attempts have been made to correlate hearing loss with inner ear pathology.[21-29] Some individuals have found more cell damage than was expected on the basis of the audiogram,[23-25] while others have noted less cell damage than the hearing thresholds seemed to indicate.[26,27] Some studies have reported no correlation at all between hearing loss and sensory cell loss[28,29]

A number of variables such as experimental animal, exposure conditions, and length of recovery may have contributed to the differences in correlation which have been reported. In addition, the strategies used by various investigators to select test frequencies and to assess anatomical damage in the ear could easily produce different estimates of correlation in the same experimental animal. For example, if animal 285 had been tested at the traditional one-octave intervals, no PTS would have been observed even though a significant PTS actually occurred. Similarly, while our initial testing strategy allowed close observation of threshold shifts in the 4-8-kHz region for animal

285, it overlooked the possibility of permanent losses in the 1-4-kHz region.

The criteria used to count damaged and degenerated sensory cells and the methods used to report the histological findings have not been standardized across laboratories. If the method of averaging cell loss over the apical, middle and basal turns[21] had been used for the ears in the present study, the high-frequency lesions in these specimens would not have been obvious at all.

The results presented here indicate that the correlation between hearing loss and sensory cell loss is dependent upon the region of the organ of Corti under evaluation.

Cell loss can be greater than the audiogram indicates. In the trained animals, OHC loss was found to average 20% and 15.7% in the low-frequency region of the 9- and 18-day groups, respectively. However, only one of these animals had a small permanent hearing loss at 0.715 kHz. This finding is not entirely surprising. Miller et al[30] found no PTS in a group of cats in which the supporting cells in the apical half of the cochlea were moderately to severely injured. Other studies have reported that small to moderate losses of hair cells can be found in ears in which no PTS is measurable. However, none of these earlier studies specified the location of the sensory cell loss.[10,15] In addition, Fried et al[6] and Bohne[7] found OHC losses in the apex of the chinchilla cochlea following exposure to a noise previously shown to produce no PTS.[10]

The findings of Bredberg[23] in the human, as well as those reported here, indicate that the entire OHC complement in the apex of the cochlea is not necessary for the detection of low-frequency tones. It remains to be determined whether any other psychophysical measure, such as frequency or intensity discrimination, is affected in ears where there is loss of OHC but normal sensitivity for low-frequency tones.

Cell loss can be less than the audiogram indicates. Animals 285 and 313 both had PTS for some of the high frequencies but neither had significant sensory cell loss in the basal turn of the cochlea. Previously, Hunter-Duvar and Elliott[27] reported PTS of 10-20 dB at 2-6 kHz in squirrel monkeys exposed to 2-kHz pure tones. These animals had no significant loss of sensory cells in the high-frequency region of the cochlea.

Cell loss can correspond to the audiogram. Animals 286 and 329 had notches in their audiograms and discrete lesions in their inner ears. The lack of exact correlation between the audiogram and damage in the organ of Corti may be due to the necessary approximations involved in constructing a frequency-place map.[13]

In contrast to cell loss in the apex, moderate cell loss in the basal turn always produced a PTS when corresponding frequencies were tested. The presence of PTS in the high frequencies when sensory cell losses are minimal is understandable. The cochleograms included in this report indicate the number and location of missing sensory cells only. The presence of a cell should not necessarily be taken to indicate that it is functioning normally. A detailed microscopic examination of the ears with PTS and no cell loss will be conducted in an attempt to identify more subtle histological indicators of cell dysfunction.

Absolute Sensitivity. Whereas Miller[8] reported normal sensitivity for the chinchilla to be about 2 dB SPL at 0.715 kHz, the average sensitivity of our animals at this frequency was 21 dB SPL. Differences in absolute sensitivity between the two groups of animals were smaller at the frequencies above 0.715 kHz and were insignificant above 2 kHz. Although there is no clear explanation for the large discrepancy at 0.715 kHz, several factors could have contributed. The acoustic system and calibration procedures used in the two experiments were entirely different. By placing the speaker at the side of the test booth rather than overhead, we may have introduced a calibration difference due to the position of the pinna and the angle of incidence of the sound source.

In attempting to identify the cause of threshold elevation at low frequencies, it was noted that the feeder produced a loud click when it was operated. The click measured 107 dB peak-to-peak at the position of the animal's ear, with a 35 msec duration. Eldredge* has observed in anesthetized chinchillas that contraction of the tensor tympani provides about 15 dB of attention at 0.715 kHz. The contractions lasted for approximately ten seconds. Since the intertrial interval averaged about five seconds, it is possible that the thresholds were elevated at low frequencies by the action of the middle ear muscles. The click may have also produced a small TTS.

It is unlikely that the low-frequency signals were masked by noise either in the booth or in the audiometric system since the booth noise exceeded 20 dB SPL only in the one-third octave bands below 50 Hz, and the hum and noise in the audiometric system was 3 dB SPL (20 Hz-20 kHz).

Although our baseline thresholds were higher than Miller's[8] and threshold shifts less than those reported by Carder and Miller,[10] the average level to which the thresholds shifted in our experiment (53.5 dB SPL at 0.715 kHz) is similar to that reported by Carder and Miller (48.65 dB SPL at 0.715 kHz).[10] In future experiments, differences in absolute sensitivity will be examined in order to determine whether they can be accounted for on the basis of acoustic differences alone, or whether more subtle physiological and psychoacoustic differences are also involved.

The 4-kHz Notch. Several theories have been advanced to explain the origin of the 4-kHz notch in the audiograms of noise-exposed humans.[31] It has been argued that the blood supply to the cochlea is somewhat deficient in the 4-kHz region of the basilar membrane so that hypoxia would affect this region first.[31] In the chinchilla, the blood vessels are generally absent at the basal end of the organ of Corti,** a region of the cochlea which was never damaged in this series of animals. Thus, our results do not support a vascular deficiency theory for the production of the 4-kHz notch.

Another theory states that the resonance of the external ear is responsible for the 4-kHz dip. The resonance in humans is such that the sound pressure of frequencies between 3 and 4 kHz is 15 to 20 dB greater at the tympanic membrane than in the sound field.[32] Thus, exposure to noise which includes energy in the 3-4 kHz range puts more stress on the high-frequency region of the basilar membrane, presumably resulting in damage to this area first. Support for this theory comes from the work of Ouchi[33] and Caiazzo and Tonndorf.[34] In both studies, humans exposed to broad-band noise developed TTS which reached maximum values at 4 kHz. When the ear canals of the subjects were artificially extended, thus lowering the resonant frequency of the canal, the maximum TTS occurred between 1 and 1.5 kHz.

Like man, the chinchilla also has an external ear which provides approximately a 15-dB gain at 4 kHz.[35] Analysis of the spectrum of the noise used in the present experiment showed that its level at 4 kHz did not exceed 55 dB SPL. Since it has been shown previously that exposure of chinchillas to a 4-kHz OBN at 65 dB SPL for nine days produced no sensory cell loss in the inner ear,[7] the high-frequency effects seen in this experiment could not have been produced by the energy of the noise in the 4-kHz region.

Evidence from a number of other studies also support this contention. Miller et al[30] noted TTS at the high frequencies in cats which were exposed to low-frequency noise. Mills et al[36] reported similar results in humans. Recently, small PTS at 2 kHz were observed in chinchillas following exposure to an OBN centered at 0.063 or 1.0 kHz.[37] These behavioral observations, along with the anatomical findings of Fried et al[6] and Bohne,[7] all suggest that injury or sensory cell loss can occur in the high-frequency region of the inner ear even when the only significant energy in the exposure is in the low frequencies.

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*Eldredge DH: Personal communication.

**Bohne BA: Unpublished data.

Strial Atrophy from Noise Exposure. Few studies have reported the condition of the stria vascularis following excessive exposure to noise. Occasionally, changes have been found in the vessels of the stria shortly after termination of the exposure. In some cases, the vessels were devoid of red blood cells,[38] while in others, they were packed with red blood cells.[39] Although these changes are presumed to be temporary, it has been postulated that prolonged vasoconstriction may lead to strial atrophy.[40]

Duvall and associates[41,42] observed swelling of the intermediate cells of the stria following exposure to noise at 123 dB for 15 minutes. The functional significance of this finding is unknown. The intermediate cells had normal appearances 28 days following the exposure.

Covell and associates[43-45] reported that strial atrophy was rarely encountered in a large series of guinea-pig ears exposed to intense pure tones for short durations. When present, strial changes were generally found in animals which had recovered for several weeks or months following the exposure. The strial atrophy was always found in the basal turn of the cochlea.

Johnsson and Hawkins[46] studied the ears of 12 guinea pigs which had been exposed to wide-band noise at 118-120 dB SPL for 8 to 110 hours. The duration of postexposure survival was not specified. Strial changes were seen in two animals exposed for 30 hours and one exposed for 110 hours. By phase contrast microscopy, the areas of strial damage appeared less densely stained (less osmiophilic) than normal. By electron microscopy, the nuclei of the marginal cells were found to be pyknotic. Some of the basal processes of the cells had disappeared and the mitochondria were reduced in number.

Fried et al[6] found regions of strial atrophy in seven out of ten chinchilla ears which were exposed to a 0.5-kHz OBN at 95 or 103 dB SPL for nine days and allowed to recover for one month. It was noted that strial atrophy was not consistent in its location, extent or relation to damage in the organ of Corti.

In the present study, strial atrophy occurred in two out of eight ears exposed for nine days and three out of nine exposed for 18 days. These results tend to indicate that strial atrophy appears more frequently as the duration of exposure is lengthened. However, in another series of ears which were exposed to the same noise for 27, 36, 45, or 54 days, only a few instances of strial atrophy were found.* Thus, although degeneration of the stria can result from prolonged exposure to noise, it does not appear to occur with any regularity.

CONCLUSIONS

1. It is possible to have broad losses of OHC in the apex, at least up to 20%, without affecting the thresholds for low-frequency tones.

2. Hearing losses can occur for high-frequency tones even when sensory cell loss in the basal turn is insignificant.

3. Audiometric notches in the 4-kHz region have been produced in chinchillas by exposure to low-frequency noise. Thus, the 4-kHz notch which often appears in the audiograms of noise-exposed people is not due to some peculiarity of the human ear.

4. Considerable variability in the size and position of the high-frequency lesion was noted in ears receiving identical exposures to the 0.5-kHz OBN. The hearing loss associated with narrow high-frequency lesions may encompass so few frequencies that it would not be detected unless thresholds were tested at closely-spaced intervals.

5. An accurate assessment of the condition of the inner ear cannot be made solely on the basis of the pure-tone audiogram.

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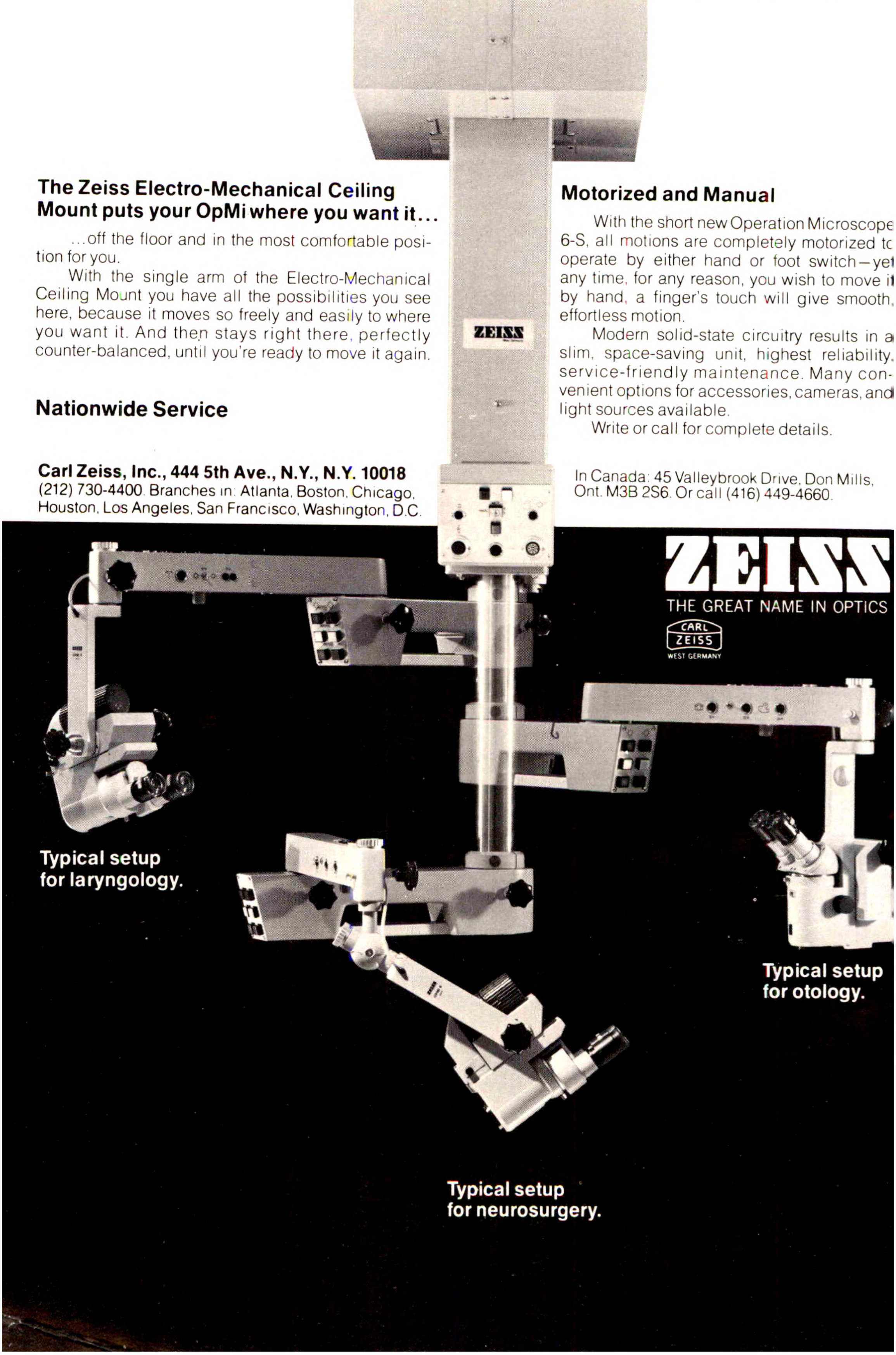

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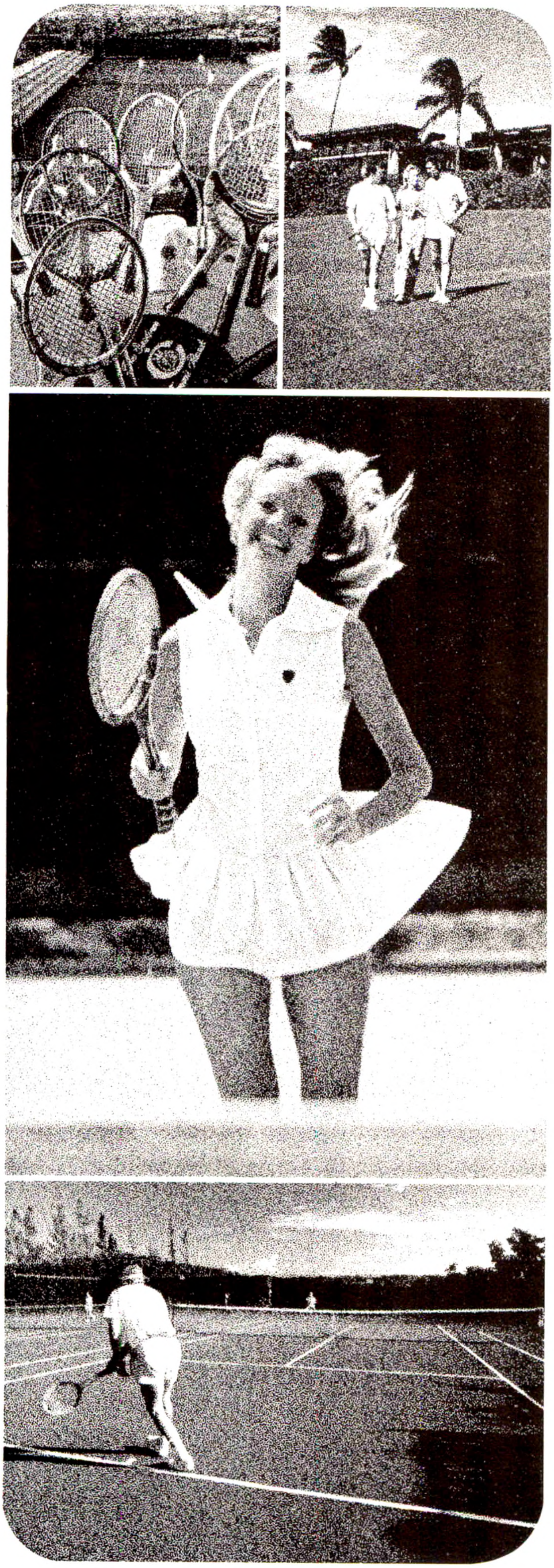

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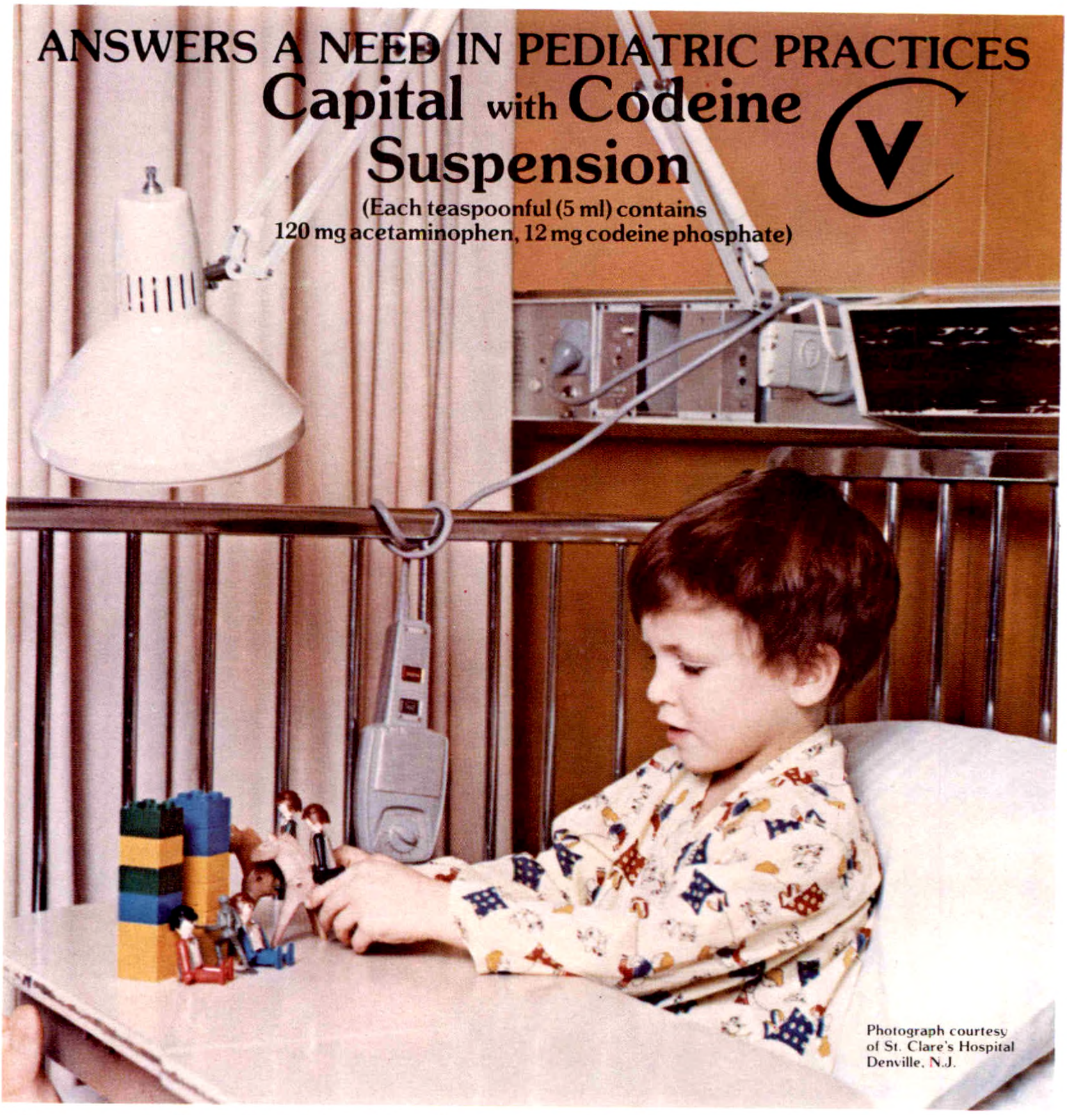

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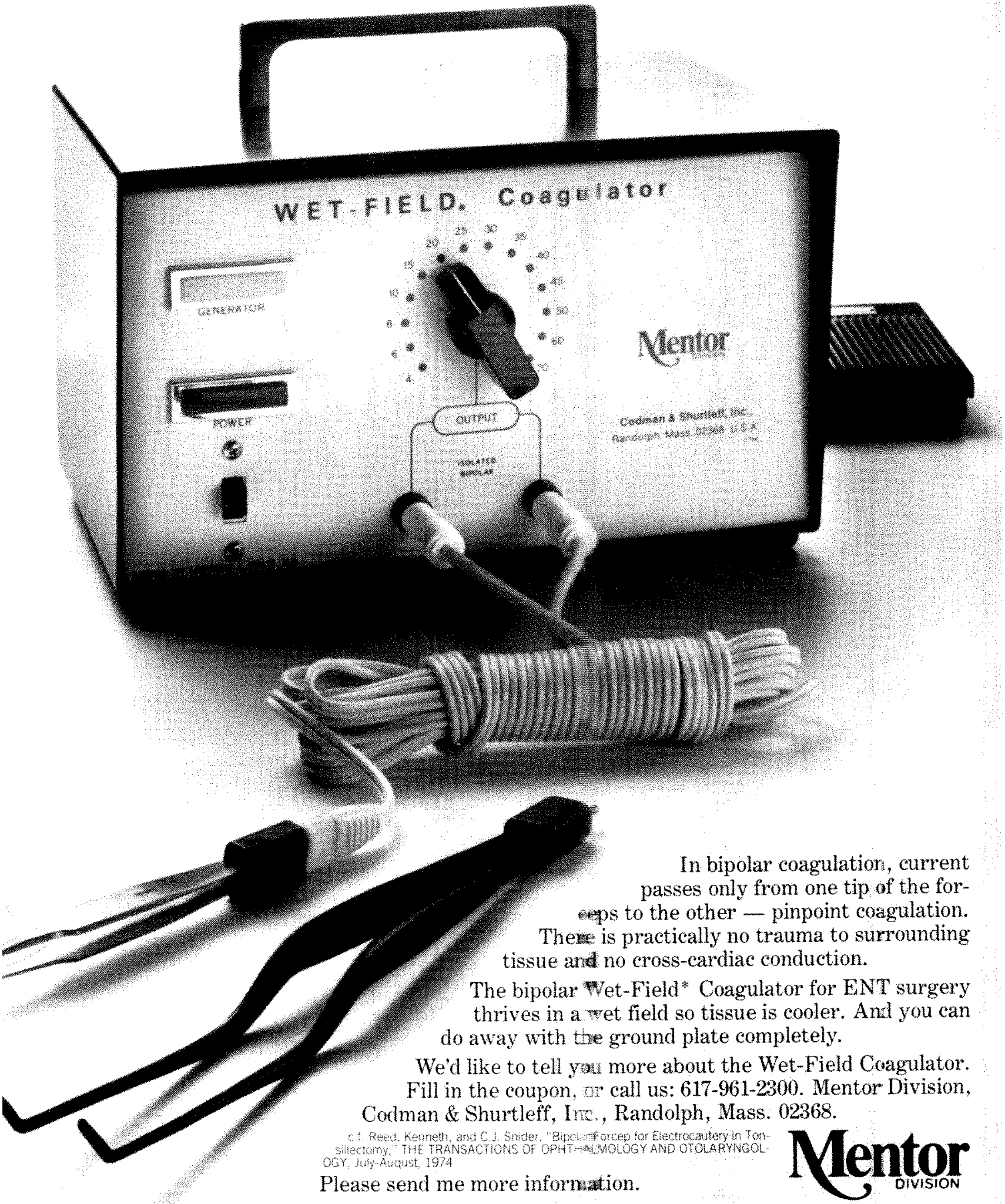

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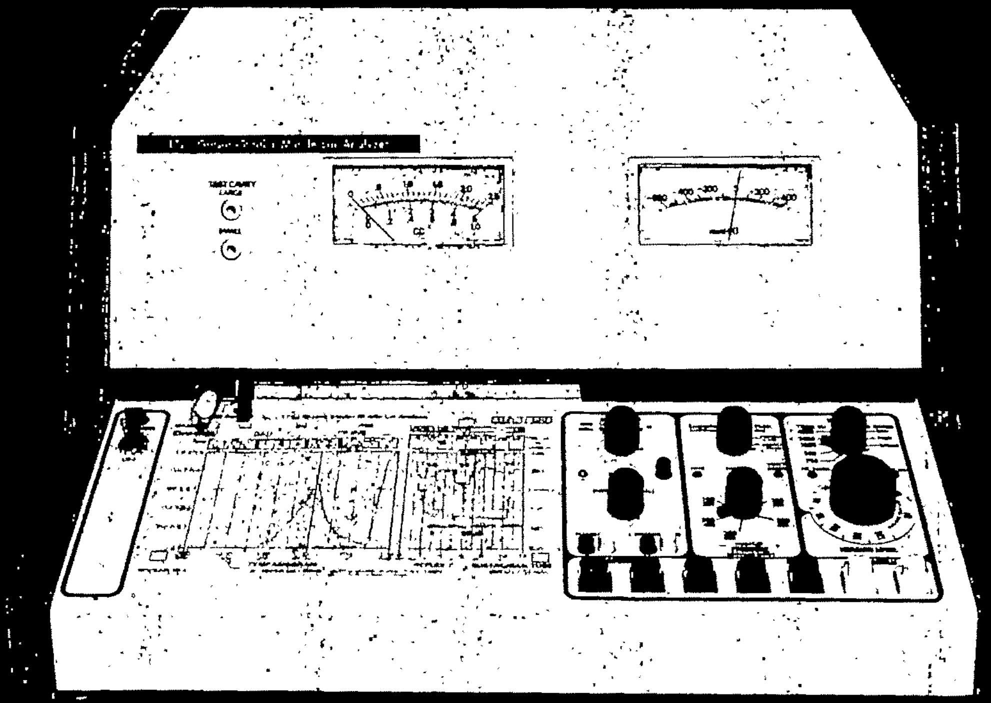

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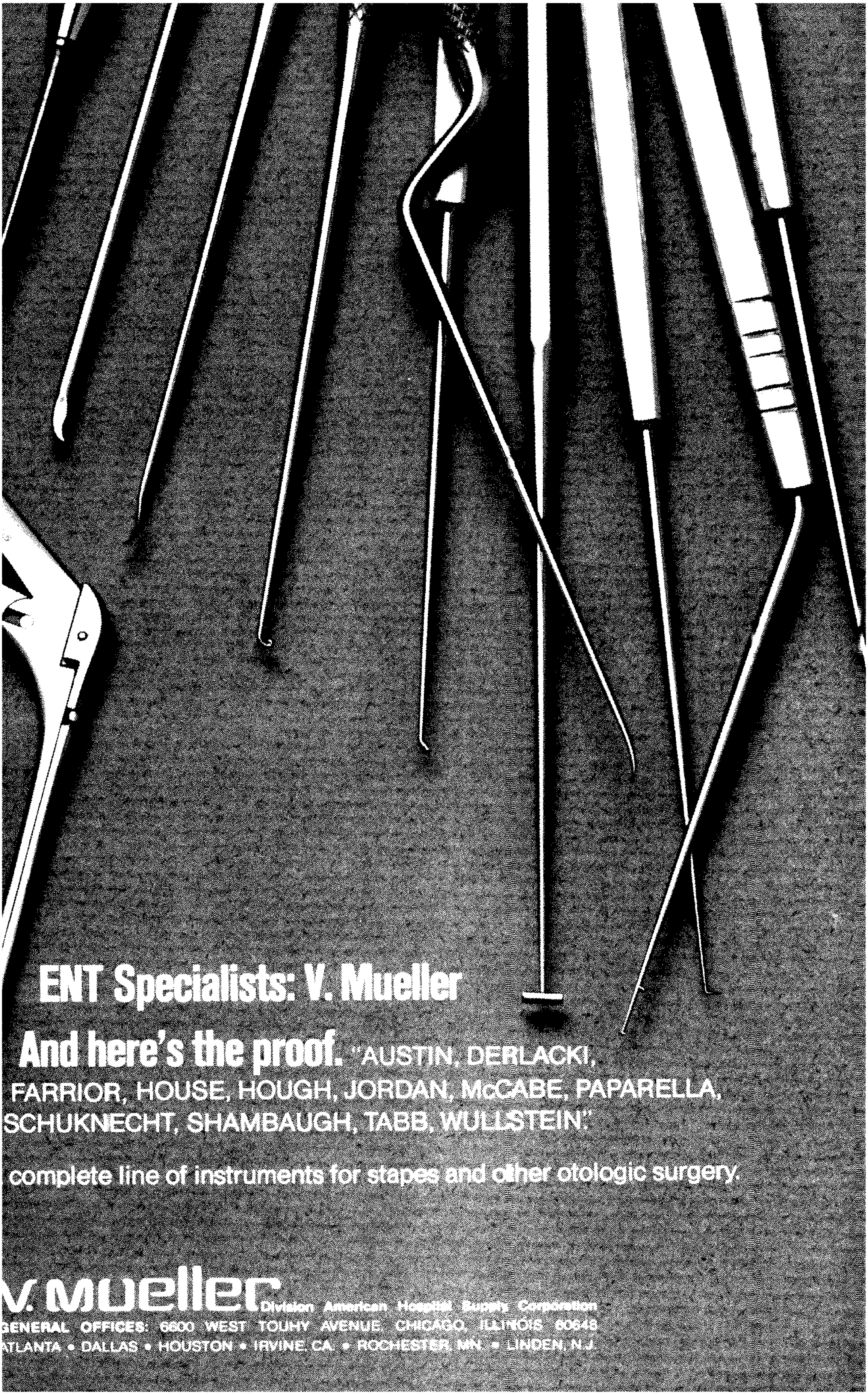

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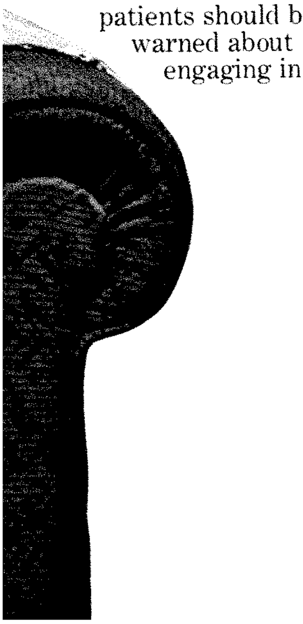

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Perennial and seasonal allergic rhinitis; vasomotor rhinitis; allergic conjunctivitis due to inhalant allergens and foods; mild, uncomplicated allergic skin manifestations of urticaria and angioedema; amelioration of allergic reactions to blood or plasma; dermographism; anaphylactic reactions as adjunctive therapy to epinephrine and other standard measures after the acute manifestations have been controlled.

CONTRAINDICATIONS
Pyribenzamine should not be used in premature infants, neonates, or nursing mothers; patients receiving MAO inhibitors; patients with narrow angle glaucoma, stenosing peptic ulcer, symptomatic prostatic hypertrophy, bladder neck obstruction, pyloroduodenal obstruction, lower respiratory tract symptoms (including asthma), or hypersensitivity to tripelennamine or related compounds.

WARNINGS
Antihistamines often produce drowsiness and may reduce mental alertness in children and adults. Patients should be warned about engaging in activities requiring mental alertness (eg, driving a car, operating machinery or hazardous appliances). In elderly patients, approximately 60 years or older, antihistamines are more likely to cause dizziness, sedation and hypotension. Patients should be warned that the central nervous system effects of Pyribenzamine may be additive with those of alcohol and other CNS depressants (eg, hypnotics, sedatives, tranquilizers, antianxiety agents).
Antihistamines may produce excitation, particularly in children.

Usage in Pregnancy
Although no Pyribenzamine-related teratogenic potential or other adverse effects on the fetus have been observed in limited animal reproduction studies, the safe use of this drug in pregnancy or during lactation has not been established. Therefore, the drug should not be used during pregnancy or lactation unless, in the judgment of the physician, the expected benefits outweigh the potential hazards.

Usage in Children
In infants and children particularly, antihistamines in overdosage may produce hallucinations, convulsions and/or death.

PRECAUTIONS
Pyribenzamine, like other antihistamines, has atropine-like, anticholinergic activity and should be used with caution in patients with increased intraocular pressure, hyperthyroidism, cardiovascular disease, hypertension, or history of bronchial asthma.

ADVERSE REACTIONS
The most frequent adverse reactions to antihistamines are sedation or drowsiness; sleepiness; dryness of the mouth, nose, and throat; thickening of bronchial secretions; dizziness; disturbed coordination; epigastric distress.
Other adverse reactions which may occur are: fatigue; chills; confusion; restlessness; excitation; hysteria, nervousness; irritability; insomnia; euphoria; anorexia; nausea; vomiting; diarrhea; constipation; hypotension; tightness in the chest; wheezing; blurred vision; diplopia; vertigo; tinnitus; convulsions; headache; palpitations; tachycardia; extrasystoles; nasal stuffiness; urinary frequency; difficult urination; urinary retention; leukopenia; hemolytic anemia; thrombocytopenia; agranulocytosis; aplastic anemia; allergic or hypersensitivity reactions, including drug rash, urticaria, anaphylactic shock, and photosensitivity. Although the following may have been reported to occur in association with some antihistamines, they have not been known to result from the use of Pyribenzamine: excessive perspiration, tremor, paresthesias, acute labyrinthitis, neuritis and early menses.

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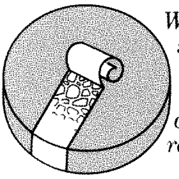

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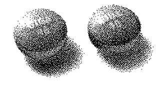

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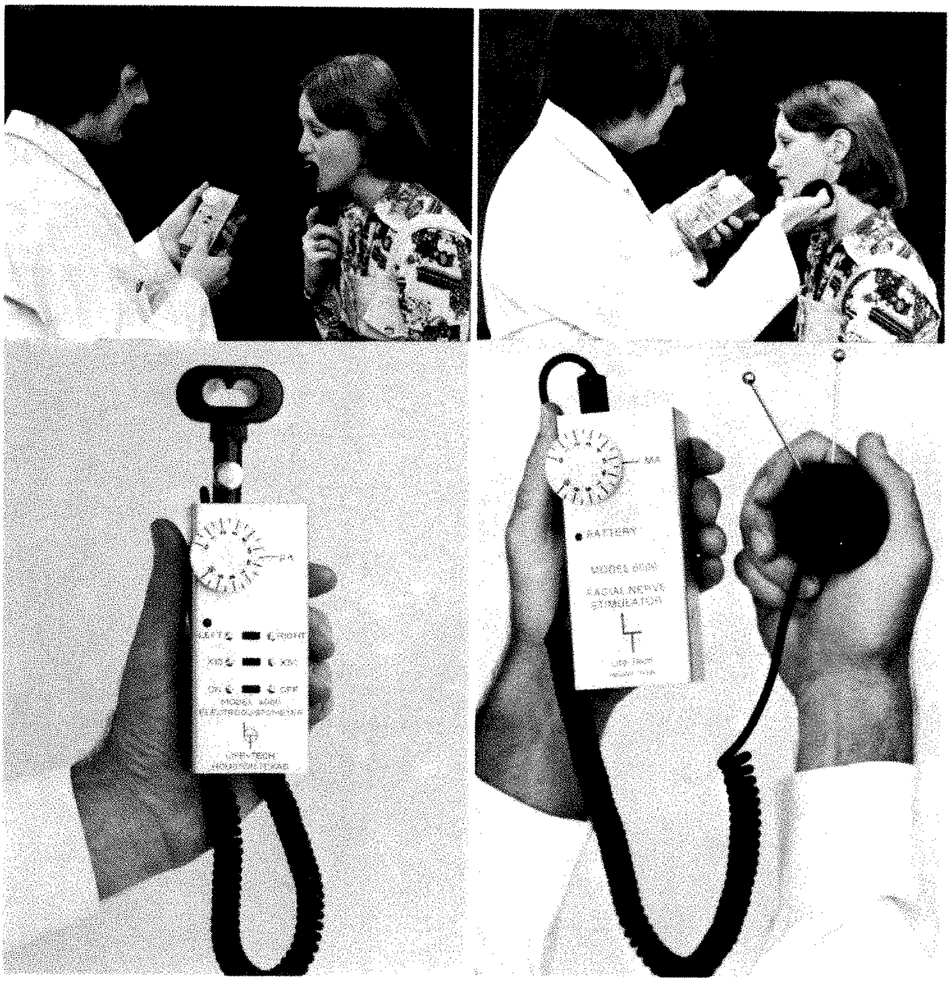

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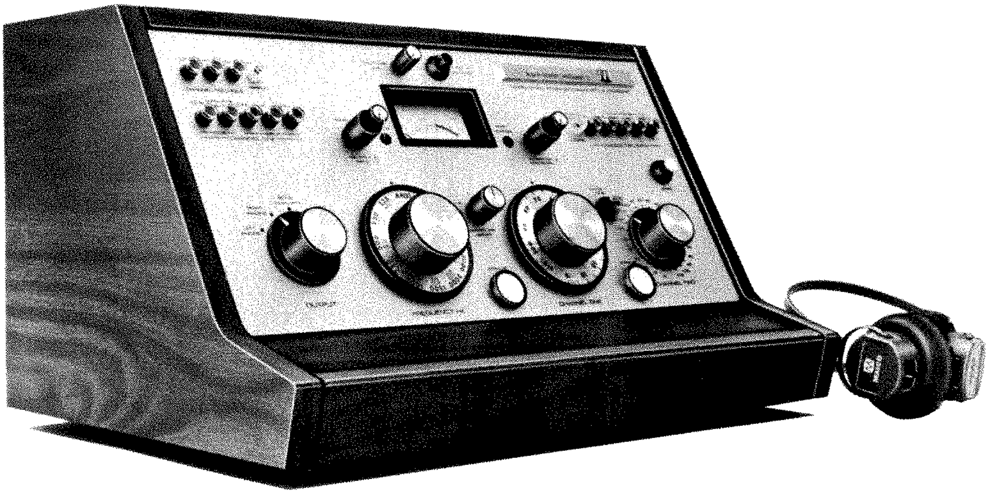

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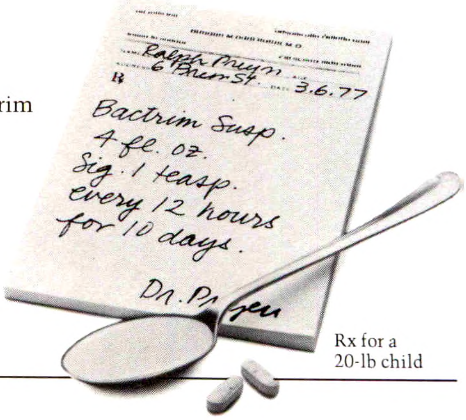

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60	27	3 teasp. (15 ml)	1½ tablets
80	36	4 teasp. (20 ml)	2 tablets or 1 DS tablet

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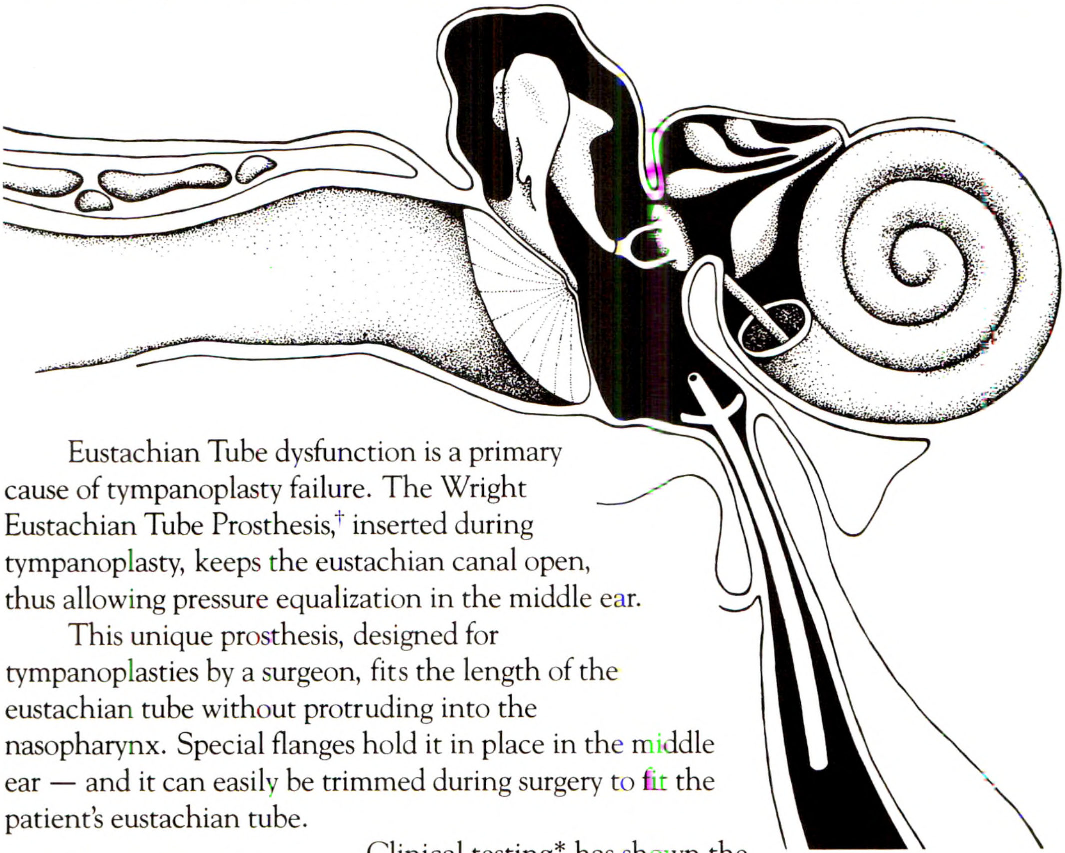

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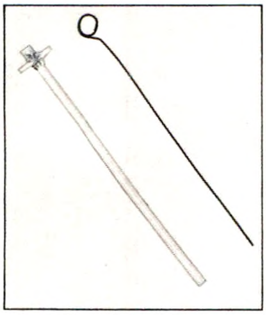

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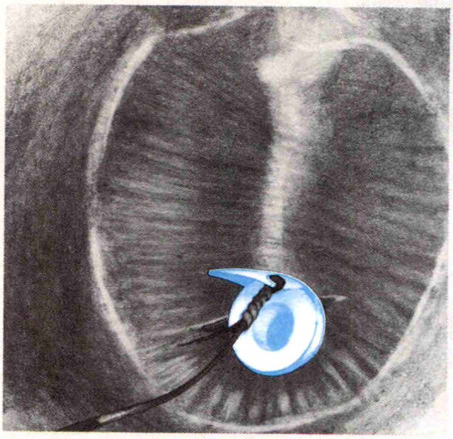

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FOURTH DANIEL C. BAKER, JR. MEMORIAL LECTURE

ENERGY AND THE LARYNX

B. Raymond Fink, MD

Seattle, Washington

Review of the logistics of energy supply in animals indicates that the advent of the larynx was part of a response to an earlier energy crisis. It permitted a major increase in the flow of energy available to the organism and became the mechanical control point and rate-limiting factor of the increased inflow. Phylogenetically, a succession of structural innovations steadily enhanced the flow capacity of the larynx and rendered the mechanism more versatile, most recently with the accrual of phonation (in mammals), pressurized closure (in primates and odontocetes), and vocal formants and efficiency (in man). The larynx is thus a marker of the animal's capabilities for energy intake, energy utilization and information emmission and, apparently, of the size and complexity of the brain. Today's energy crises appear to continue those of the past.

An anesthesiologist's point of view about the larynx is probably not quite the same as the laryngologist's. The anesthesiologist is apt to see the larynx as an inconvenience, and occasionally even wishes it had never been invented. In milder moments he thinks of sound production by the larynx as a reprehensible aberration and does his best to suppress it. In the course of an old-fashioned stormy induction, he might encounter incoherent babbling, excited shouting, retching, vomiting, swallowing, coughing, musical glottic noises, ominous guttural stridor, complete occlusion, or sometimes even simple, smooth depression of the respiratory movements. Thus it seems that the larynx of an anesthetized person is liable to a unique range of functional mishaps, apparently stemming from its dual role as a portal of energy inflow and information outflow.

Energy and information, yes, but energy is the ultimate irreducible riddle. Without the flow of energy there would be neither time and space, nor information of any kind. Energy flow underlies everything we experience or imagine, it dominates the physical universe and all the phenomena of life, including intelligence. The larynx, as we shall see, takes a strategic part in this flow, a part that gives me the chance to ask a seemingly irrelevant question. Why are there no intelligent worms, no intelligent insects? Insects have had just as long to evolve as we have, nay much longer. In answer, let me briefly sketch the history of energy flow in animals, beginning with its antecedents in single cells.

ENERGY PROCUREMENT IN LOWER INVERTEBRATES

The energy flow that underlies all the myriad transactions of animal metabolism is, of course, derived from the oxidation of foodstuffs. The principal energy-yielding reactions are oxidation-reduction reactions that rely on oxygen as the oxidant and molecules derived from food as the reductant. The oxidant is plentiful and freely available in the biosphere, but the reductant is in short supply. In general, animals have to forage for their reductants. At a still relatively simple level of animal organization the oxidant diffuses in through the entire surface of the organism but the entry for reductant is restricted to

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From the Department of Anesthesiology, University of Washington, Seattle, Washington.

Presented at the meeting of the American Laryngological Association, Palm Beach, Florida, April 22-23, 1978.

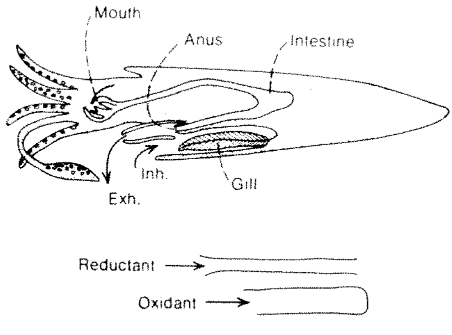

Fig. 1. Scheme of energy inflow in a mollusc, the squid (*Loligo*). The oxidant and reductant substrates gain entry through separate channels.

a small region, the mouth. Illustrative of this system of energy procurement are protozoa. But neither protozoa nor our next group, the coelenterates, have an oxidant supply system as such. The respiratory gases simply diffuse in and out passively.

The coelenterates, however, procure reductant with the aid of a nervous system. It is no exaggeration to say that this is the primary role of an animal's nervous system, since many, if not all, of the activities of the animal are directed to the maintenance of energy flow. The energy, of course, is used for the maintenance or growth of the organism, whether growth in size, storage growth, replacement growth, or growth in numbers is immaterial. In this sense, all organisms are programmed to grow indefinitely. From an energy flow point of view, they are power systems, each one of which is programmed to go on growing without limit. From the power viewpoint, infinite greed is a characteristic of every form of life.

ENERGY PROCUREMENT IN HIGHER INVERTEBRATES

In animals more complex than coelenterates, the energy supply system includes a neural program for the procurement of oxidant as well as one for the procurement of reductant, and uses a special surface, a gill, for the extraction of the oxidant oxygen from the environment. There is also a pump for circulating the environment, in this case water, past the extracting surface. This type of supply system is found in higher invertebrates (nonchordates), the molluscs (Fig. 1) and arthropods, and from a logistic point of view may be summarized as ingestion in parallel. Reductant and oxidant are ingested through different orifices. These animals can, in principle, feed and breathe simultaneously and continuously, and all of them have a relatively poorly developed central nervous system (CNS). They exhibit a low degree of encephalization and a limited intelligence. Why? Remembering that the energy demand of the human brain accounts for almost 20% of the energy utilized by the body, we might suggest that one reason why animals such as insects have never developed a high I.Q. is that their energy procurement system is not capable of sustaining one. Apparently there was no possibility of developing a higher intelligence until a better energy procurement strategy had come about, as happened in the chordates.

ENERGY PROCUREMENT IN CHORDATES

In the chordates, this includes all the vertebrates, the flow plan of the energy supply system is radically different. The oxidant and reductant supplies are obtained, not in parallel, but in series. This scheme is well-illustrated in the most primitive living prototype of chordates, *Amphioxus* (Fig. 2). *Amphioxus* may be summarized as an energy-collecting funnel driven through the water by the rest of the body. The mouth of the funnel takes in water containing gaseous oxidant in solution and solid reductant in

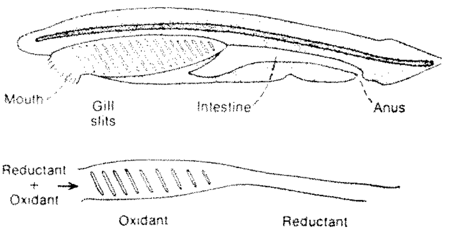

Fig. 2. Scheme of energy inflow in a primitive chordate, (*Amphioxus*). Oxidant and reductant enter through a single orifice and are absorbed in series.

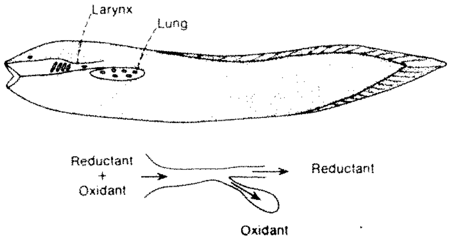

Fig. 3. Energy inflow in a primitive air-breathing chordate, the African lungfish, (*Protopterus*). The larynx and hypopharynx mark the parting of the ways for gaseous oxidant and solid reductant.

suspension and, propelled by cilia, these eventually reach their appropriate extractors, first the gill slits and then the gut. Note that as yet there are no jaws, no mandibular force pump. Relative to the mouth, however, the extractors are in series, a relationship they owe to their origin in the dim past in the protochordates. The important point is that with this logistic plan, all substrates are swept in through a single orifice and the animal is faced with a question and a decision, so to speak, every time something enters the mouth: Oxidant or reductant? Oxidant? Go gill. Reductant? Go gut. This fundamental choice, the focal "go" of the chordate scheme of things, is extremely rudimentary in *Amphioxus*, but never arises at all in a nonchordate. In nonchordates, oxidant and reductant are absorbed in parallel and there never has been any possibility of a larynx.

The chordate-become-vertebrate fish, of course, is not yet ready to evolve a larynx. First came jaws and the buccal bite and gulp, a clever energy-grabbing device that both needs and makes possible a lot more brain. The brutal efficiency of this arrangement is seen with stark simplicity in a gnathostome fish. The buccal energy grabber is also a powerful pump, propelling the oxidant solution and the reductant solids to their respective extractors; but the pump has a limited range of action and the gill slits, now become gills, are restricted to its immediate neighborhood.

ENERGY LOGISTICS WITH A LARYNX

The motorized collecting funnel can now discover the huge oxidative potential contained in a mouthful of air and take advantage of it by forcing the air into a lung (Fig. 3). When it does so, the choice inside the mouth of our ancestral air breather becomes a choice of three: go gut, go gill, or go lung — the problem of discriminating between solid, liquid and gas. This poser has never been faced and could never be addressed by an air-breathing mollusc, such as a pulmonate snail, or an air-breathing arthropod, such as a spider. The lung in these animals opens onto the surface of the body, far away from the orifice of the mouth. In them the risk of clogging the lung with food does not exist, and the brain is not bothered with a choice of internal routes. However, in vertebrates, the advent of a lung necessarily means the advent of a

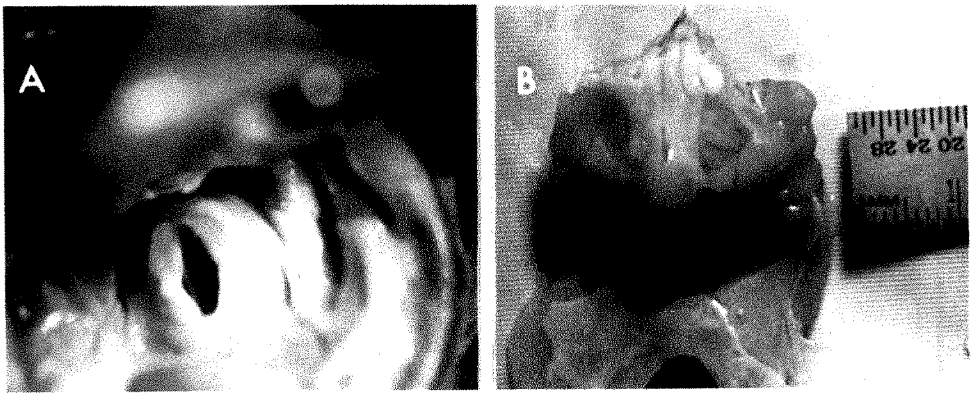

Fig. 4. The larynx in an amphibian, the bullfrog; buccal view. A) Inspiratory effort: the laryngeal orifice has opened by outward tilting of the arytenoid half-domes. B) Relaxed larynx is closed and dome-like.

TABLE 1. LARYNGEAL SYSTEMS: PART I

Lungfish	*Urodele*	*Anuran*	*Reptile*	*Bird*
	Arytenoid	Arytenoid	Arytenoid	Arytenoid
		Cricoid	Cricoid	Cricoid
			C-A joint	C-A joint
				Syrinx

C-A - Cricoarytenoid.

larynx and brings into play a new mechanical focus, a bifurcation in the energy supply system. The new mechanical focus comprises the larynx and pharynx, a valve where, henceforth, gaseous oxidant and nongaseous reductant and water are routed to their respective absorbers.

The control valve (it has no name, but "phlarynx" would be a handy one) constitutes a bottleneck that limits, or from time to time interrupts, the inflows of oxidant and reductant. "Phlarynx" is not merely a catchword; for the brain it is apparently a real functional entity. Its propulsor muscles, the constrictor muscles of the pharynx and the intrinsic muscles of the larynx, are all supplied by the same nerve, the vagus, and indeed the same nucleus of nerve cells, the nucleus ambiguus, a nucleus that supplies almost nothing else and whose phylogenetic development parallels the differentiation of the muscles. Interestingly and curiously enough, the territory of the rest of the vagus nerve is restricted to the lungs and the gut, the absorbers of energy, and the heart, the distributor of energy.

The rhythms of inflow of the two major energy substrates differ. The inflow of reductant is intermittent. I take it that all of us at the moment have interrupted our reductant inflow. But our inflow of oxidant, our breathing, in contrast, goes on continuously. Clearly, the rate-limiting factor in the inflow of energy is the flow of oxidant. That being so, in air-breathing vertebrates the larynx becomes the rate-limiting mechanical control point in the flow of energy through the organism which, if one views the CNS as an energy computer, is tantamount to saying that the larynx becomes the focal mechanical control point of the nervous system.

A lot of other things, of course, are demanded of the nervous system besides controlling the larynx, just as a lot of other things change in the course of vertebrate evolution besides the pharynx. Nevertheless, the coordinating and integrating force underlying the changes is the phenomenon of energy flow. What matters here is that there is now a larynx-plus-pharynx which, from the moment it appears on the scene, constitutes both a master control point and a modulatable bottleneck in the energy flow system. As such, it becomes a manifestation, an indicator, or, in current jargon, a marker of the energy flow capabilities of the organism.

Mammals. I will skip through the amphibian and reptilian grades of larynx (Fig. 4 and Table 1), although each introduces engineering innovations that promote an ampler flow of gas, and will concentrate on our own order, the mammals (Table 2). Here the oxidant bottleneck becomes dramatically enlarged by the addition of a thyroarytenoid complex, namely the thyroarytenoid folds along with their supporting thyroid cartilage and protective epiglottic cartilage. The primary benefit of the folds is a freer energy flow, but they also have

TABLE 2. LARYNGEAL SYSTEMS: PART II

Monotreme	*Marsupial*	*Placental*
Arytenoid	Arytenoid	Arytenoid
Cricoid	Cricoid	Cricoid
C-A joint	C-A joint	C-A joint
Epiglottis	Epiglottis	Epiglottis
Thyroid cart.	Thyroid cart.	Thyroid cart.
C-th junction	C-th junction	C-th junction
	Th-ary. Fold	Vestib. fold
		Vocal fold

Cart. - Cartilage; C-th - Cricothyroid; Th-ary - Thyroarytenoid.

an inherent potential for the generation of sound.

As before, much besides the larynx is involved in these developments, yet the larynx remains and constitutes the focal mechanical control point of the apparatus as a whole. Cause? Effect? Coincidence? Be that as it may, every increment in the properties of the control valve seems to correlate with an increase in complexity and size of the CNS. This is true up to the monotreme and marsupial levels I have been describing, and it is also true of the later increases in laryngeal conductance we are about to examine.

The next functional development in the history of the larynx was the emergence of modulatable vocal activity. This behavior demands the ability to vary the tension of the thyroarytenoid fold, which in turn necessitates the presence of a synovial cricothyroid joint and a cricothyroid muscle and the subdivision of the thyroarytenoid fold into vocal and vestibular sectors. Both sectors are activated for protective closure of the larynx, but only the vocal folds' sector is activated for phonatory behavior of the glottis. These developments, the synovial cricothyroid joint and muscle and the subdivision of the thyroarytenoid fold, are not to be found in monotreme or marsupial mammals, but only in the placentals, who therewith gain a capacity for flexible vocalization. What this means is that the primary mechanical control for the inflow of energy becomes, in addition, the primary mechanical control for the emission of information. This is a crucial innovation in the animal kingdom. The emission of information, of course, is not what is new. A squid that emits a cloud of ink emits a cloud of information, or perhaps, misinformation. What is new is that the already modulatable focus of the energy inflow system expands into an additionally modulatable focus of information outflow. This gives the CNS a doubly complicated job, or, viewed backwards, it gives the vertebrate CNS an opportunity to develop hugely compounded complications that simply never exist in a nonvertebrate.

TABLE 3. LARYNGEAL SYSTEMS: PART III

Monkey	*Ape*	*Man*
Arytenoid	Arytenoid	Arytenoid
Cricoid	Cricoid	Cricoid
C-A joint	C-A joint	C-A joint
Epigl.	Epigl.	Epigl.
Thyr. cart.	Thyr. cart.	Thyr. cart.
C-th joint	C-th joint	C-th joint
Vestib. fold	Vestib. fold	Vestib. fold
Vocal fold	Vocal fold	Vocal fold
Th-hy sac.	Thyrohyoid fold	Thyrohyoid fold
		Bernoulli rima

Epigl. - Epiglottis; Vestib. - Vestibular; Thyr. - Thyroid; Th-hy - Thyrohyoid.

We are not surprised to note that the superiority of vocal equipment of the placental mammals coincides with further striking development of the brain, notably the advent of a corpus callosum and considerable expansion of the neocortex.[1]

Primates. Continuing this selective survey, we observe next that certain groups of placental mammals who have a use for high subglottic pressures have developed ways of temporarily reinforcing the closure of the glottis to prevent the escape of pressurized gas. I have in mind first the primates who live in trees, and their relatives who have reinvaded the surface of the land (Table 3).

Man is, of course, one such animal. In him a median thyrohyoid pad of

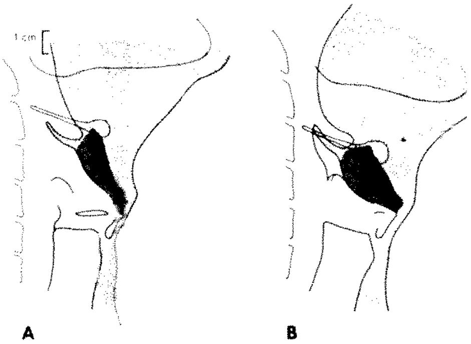

Fig. 5. Lateral x-ray tracings of neck region of a man, show the compressibility of the median thyrohyoid tissue (striated). A) Eupneic expiration; B) Effort closure.

tissue can be forced against the top of the adducted thyroarytenoid folds so as to withstand even the strongest pressure from below (Fig. 5). The buildup of subglottic pressure during the expulsive efforts of coughing or childbirth is familiar, as is the buildup during supportive efforts to stiffen the trunk for punching or kicking or lifting a heavy weight.[2] X-rays show that in great apes, too, the larynx is capable of something very like the human type of effort closure, and anatomical analogy suggests the same is true for monkeys (Table 3), although in these the closure must be less solid since the thyrohyoid space is occupied by an air sac rather than by a solid plug. Very likely, in apes and monkeys, effort closure comes in handy for strong locomotor efforts in the trees. Note that the range of closing pressures required in a monkey surging through the trees is probably smaller than in an ape who can both travel in the trees and stand on the ground and lift weights with his hands.

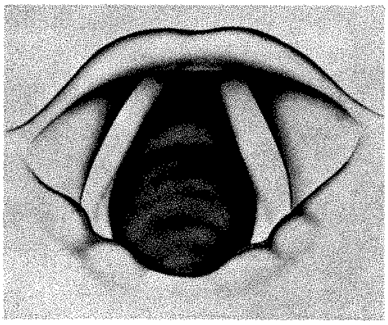

Fig. 6. The glottic pentagon of the human larynx in deep inspiration, photographed through a mirror. The pentagonal outline of the glottis is formed by the vocal ligaments, the vocal processes and the interarytenoid tissue. (Redrawn from Bell Telephone film.)

Another conspicuous modification of the larynx in primates is that the open glottis has a pentagonal outline (Fig. 6) rather than the nearly quadrilateral one present in other mammalian orders. What seems to happen is that inspiratory descent of the larynx pulls the arytenoids laterally to produce a five-sided opening. In any case, it is clear that, whatever the mechanism, enlargement of the glottic bottleneck to a pentagon allows a bigger flow of oxidant, and the enlargement coincides admirably with the presence of an effort closure mechanism that intensifies the degree of exertion. That is to say, in the monkey, and still more in the ape, the pentagonal glottis improves the efficiency of energy inflow, while the median thyrohyoid fold and effort closure improve the efficiency of energy utilization. The essential point is that in the primates the larynx, which began as a mechanical control of energy inflow and later added mechanical control of information outflow, has acquired an additional function, that of mechanical control of energy utilization. Once again, every accession of laryngeal function seems to bring with it a further accession in cerebral agility. From this it is but a step (but what a step!) to propose that mammalian cerebral agility (in the figurative sense) and mammalian laryngeal agility (in the literal sense) always evolve hand in hand. Support for this proposal comes from an unexpected quarter.

Odontocetes. Besides the primates, at least one other major group of mammals has developed prominent laryngeal specializations adaptive to intense physical efforts and an absolutely gas-tight closure of the larynx. I refer to the order of odontocetes, the whales, dolphins and porpoises, some of which are known to dive to depths of 450 meters (1,500 feet) and beyond. In these animals the flexibility of the rib cartilages allows the chest wall to cave in harmlessly under hugely increased hydrostatic pressure. The pulmonary alveolar gas is squeezed into the bronchi and trachea and the absorption of nitrogen is prevented. This behavior forestalls any risk of the bends but clearly requires a firm, totally leakproof, yet voluntarily regulated closure of the airway. The larynx of the odontocetes has obliged in a quite remarkable manner.

The epiglottis of odontocetes roughly resembles an elongated cone cut in half along the vertical axis. The cuneiform cartilages look somewhat like elongated quarter cones, so that when the animal

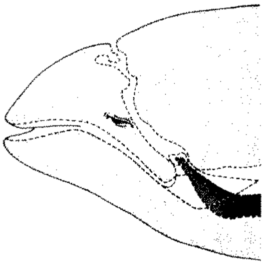

Fig. 7. Closure of the larynx in a porpoise.[3] The cone formed by the apposed epiglottic and cuneiform cartilages is elevated and gripped by the stylopharyngeus muscles at the back of the pharynx. (Redrawn from Negus).[3]

closes its larynx, the assembly of epiglottis and cuneiform cartilages forms a tapering solid (Fig. 7) whose tip can be tucked into the postnasal ring of muscle behind the soft palate. Whether this does in fact happen during diving is not known for certain, although it does happen during the induction of anesthesia, as Dr. Eugene Nagel has observed.*

Negus[3] felt that in the porpoise the arrangement of the cartilages caused difficulties in protective closure and said that this function was taken over by the valve-like flap of the blowhole. However, another interpretation is possible. We know that the intranarial tip of the cone can be firmly gripped by the postnarial ring of muscle and clamped shut somewhat like the three-piece chuck of a drill, as illustrated by Negus himself. It is easy to imagine that under these circumstances, nothing could get either in or out past the apposed surfaces of the cartilages. And, indeed, as Nagel found during induction of anesthesia, this type of laryngeal spasm proves fatal to a dolphin unless the cone is pulled out of the nares of the animal by the anesthetist. Particularly noteworthy is the fact that the same streamlining of the cartilages that maximizes tightness of closure in diving also minimizes resistance to gas flow in breathing, an important advantage when the animal briefly surfaces for a swift outrush and inrush of air.

In the odontocete, then, we encounter a variant of breathholding effort closure allied to streamlined energy inflow. Though differing from that of the primates, the variant is achieved with modifications of the same laryngeal cartilages. Though differing in details of execution, it is equally beautifully adapted to the animal's system of locomotion and substrate procurement. In the odontocete the mechanism demands a peculiar variety of agility that enables its owner to grab and swallow a prey deep under water without incurring the slightest risk of drowning. Such a performance doubtless requires and utilizes a high degree of intelligence.

As is well-known, and subject to various cautions which I will not enumerate, one can very roughly grade an animal's brain from the ratio of the brain's weight to the body's weight. I have selected a few relevant data from Jerison[4] for Table 4. The table shows that by this crude criterion, porpoises and dolphins are the equals or even the superiors of the apes. But note that this degree of brain development was already present in the dolphin ancestors 15 or 20 million years ago. If the odontocetes are the apes of the sea, why didn't the odontocete stock develop a still higher form of brain on a level with man's, as happened with the primate stock? A little wistfully I ask, where are the mermaids? Where are the maids and the young men of the sea? Could it be that the odontocete variant of energy flow and effort closure precluded the development of a still more advanced form of laryngeal gymnastics and so never gave the dolphin brain a chance to evolve a merman?

TABLE 4. BRAIN:BODY WEIGHT RATIOS (gm/kg)[4]

Gorilla	5
Chimpanzee	7
Porpoise	8
Australopithecus	15
Homo	24

Of course the orthodox doctrine of cerebral evolution does not relate the advancement of the brain to the ad-

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*Personal communication.

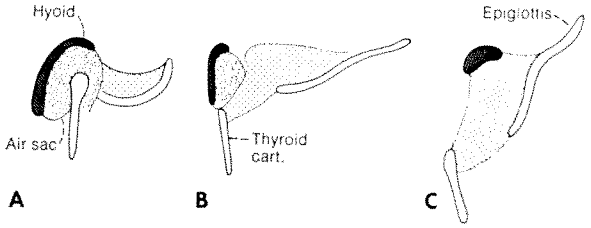

Fig. 8. Median section through cadaver specimens of the thyrohyoid junctional regional in A) An old world macaque monkey, (*Cercopithecus*), B) An ape, (*Pan*), and C) Man (*Homo*). The low station of the larynx in man is probably adaptive to formant production (see Fig. 11).[3,5]

vancement of executive organs, or relates these only loosely. In the best known case, the human, comparative anatomy likes to stress the generally unspecialized, primitive character of peripheral structures. The hand was for long the favorite example of primitiveness. But such a doctrine overlooks what is perhaps the most progressive executive organ of all, namely the larynx, and leaves out of account the central force of all evolution, animate or inanimate, namely the flow of energy.

Human Grade of Larynx. What of man? In us the larynx has acquired additional, if somewhat elusive, physical and functional attributes. The physical ones principally affect the soft tissue folds, and may be summarized as slenderness and mobility. To achieve them, nature figuratively took the preexisting primate machinery of the larynx and stretched it downward and thinned it out. The job was done by further migration of the larynx caudally and away from the hyoid bone (Fig. 8). Physically this tended to elongate and thin out the junctional soft tissue folds: the median thyrohyoid fold, and also the aryepiglottic and vestibular folds, and to flatten the last mentioned against the inside of the thyroid cartilage. Functionally this streamlined the passage for air and energy flow while mobilizing the parts and the organ as a whole for variable tonal and formant production.

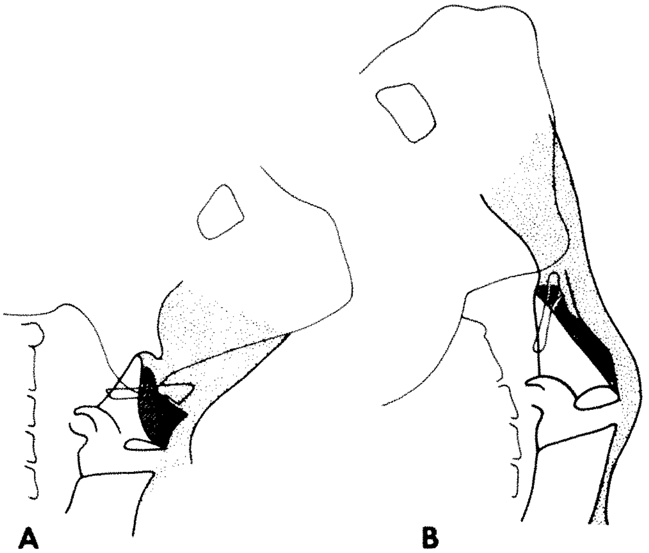

Fig. 9. Lateral x-ray tracings from an anesthetized siamang ape. A) Normal posture of head; B) Head extended. Note the remarkable extensibility of the median thyrohyoid tissue (striated).

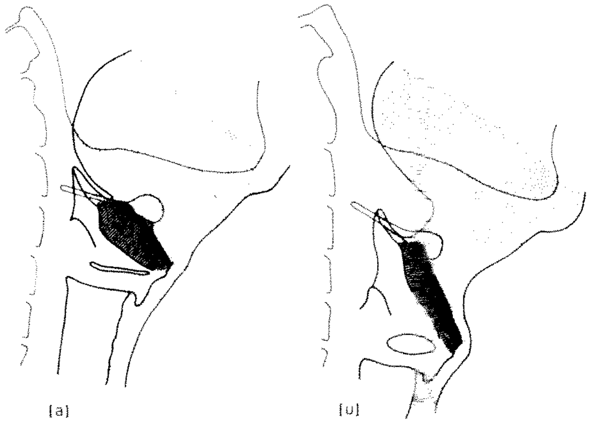

Fig. 10. Lateral x-ray tracings illustrating the behavior of the median thyrohyoid fold in phonations [a] and [u]. With [a] the station of the larynx approximates that of effort closure. With [u] the station is that of deep inspiration. The extensibility and compressibility of the median thyrohyoid fold is exploited in the production of these vowels.

The streamlining effect of stretching can be simulated after a fashion in contemporary great apes. Dr. Evan Frederickson and I demonstrated this in a still unpublished x-ray study we recently performed at the Yerkes Primate Center. In gibbons and siamangs (Fig. 9), for example, the median thyrohyoid fold profile has an almost perfect quarter circular outline, evidently well-suited to effort closure and adaptive to an effortful locomotory style of brachiation in the trees and bipedal running on the ground. By human standards a better profile for effort closure could hardly be imagined. Now observe the remarkable attenuation this fold undergoes when the animal's head is passively extended.

Note in the unstretched state, the one adapted to effort (and swallow) closure, the outline of the median thyrohyoid fold at its lower end. It meets the thyroid cartilage nearly at a right angle. This relation minimizes the shearing stresses that develop here during vertical compression of the fold in effort. In man the effort station is also used for the phonatory utterance [a] (Figs. 10 and 11), and a perpendicular relation is then unmistakable, but note that this relation could not prevail unless, in the descended inspiratory station the angle of the thyroid cartilage was already inclined forward at an angle of 30° or so. The prominence of the Adam's apple ensures that the shear-free 90° relationship will be present during effort clo-

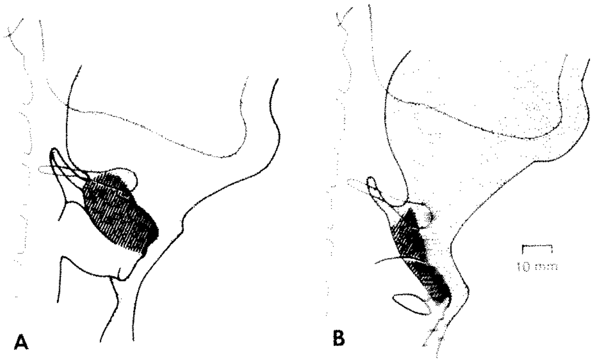

Fig. 11. Lateral x-ray tracings, illustrating the extensibility of the human median thyrohyoid tissue. A) Effort; B) Deep inspiration.

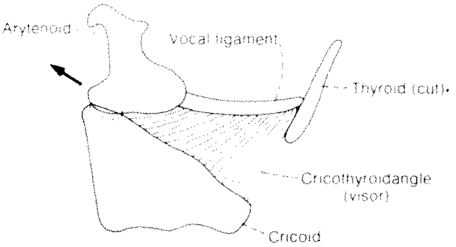

Fig. 12. Diagram of the human vocal ligament and cricothyroid membrane, right lateral view. Adduction of the arytenoid in the direction of the arrow raises the tension in the cricothyroid membrane, which in turn tends to bow the vocal ligament outward, as in Fig. 13.

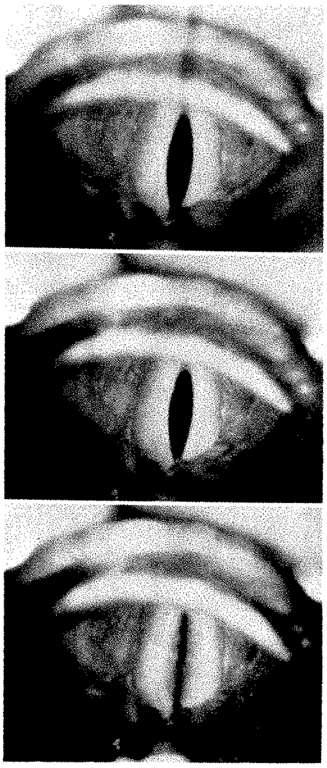

Fig. 13. The human glottis at the onset of phonation. Before vibration begins (upper two pictures), the adduction of the arytenoids has caused the vocal ligament to bow outwards, giving the rima glottidis a biconvex lenticular outline. The paramedian axis of vibration enables dynamic pressure drop to reduce the effort of initiating and maintaining conversational tones (Bell Telephone film).

sure, when it really matters. Notice further that in phonating [u] the larynx occupies the fully descended inspiratory position (Fig. 11) in the neck; observe how this stretches and attenuates the thyrohyoid junctional tissues and enlarges the respiratory passage. Clearly, the eupneic, partially prestretched condition is itself conducive to high respiratory gas flows and to a wide range of vertical modulation of the vocal resonances above the glottis. Notice, finally, that the pronounced cricothyroid "visor" angle (Fig. 12) between the thyroid and cricoid cartilages in man may be thought of as slightly prestretching the vocal folds downwards. Such an effect may well have been pregnant with consequences for the emergence of language. The stretch insures a biconvex lenticular curvature of the adducted vocal ligamentous edges. An effect of this sort is probably built into the human vocal folds by the slope of the axis of the cricoarytenoid joint. In man the axis slopes upward exceptionally steeply, as well as backwardly and medially, and the arytenoids necessarily retrace this route during closure of the glottis. As a result, arytenoid adduction automatically generates downward tension in the cricovocal membrane and lateral tension in the vocal ligament. The combined tensions produce the concavity of the medial border of the ligament, observable from above as a biconvex rima at the onset of low pitch phonation (Fig. 13). The outward curvature insures that the dynamic fall in pressure (Bernoulli effect) will come into play at the very onset of phonation and substantially reduce the work of vibrating the folds during conversation. Moreover, it is apparent that a large resting angle between the cricoid and the thyroid tends to maximize the angular motion available between the cartilages and so to augment the range of tensions and tones that can be imposed on the vocal ligaments.

We see, then, that the cervical station and prominence of the human larynx are adaptive alike to intensive oxidant inflow, to intensive effort, and to intensive information outflow. In brief, the human larynx is specifically adapted both to hard work and to speech: energy and information.

POWER

The constraints that govern energy flow and information flow, of course, underlie all aspects of evolution throughout the immense diversity of animal life. The human larynx too has had to evolve with those constraints but, in making the most of the possibilities, it has given the human brain unique opportunities to develop. I think the human degree of cerebral development was attained precisely because the human larynx contrived to focus and intensify both energy flow and information flow at a single mechanical control point.

Earlier in this talk I suggested that the overall task of the CNS is to control the energy flow of the organism. I argued that the flow of energy enables organisms to maintain themselves, grow, or multiply continuously and that in this sense all organisms are biochemically programmed to make an improvident grab for unlimited power. I would now add that their grab usually exceeds their grasp and is restrained by the limitations of the rival energy inflow and information outflow systems. Nature has evolved a balance between the biomasses of the contending power systems, a balance that expresses the efficiencies of their respective power grabs But the balance of nature is blind. These facts, if they are facts, may help us to understand a little more clearly the ultimate roots and destiny of human behavior.

Humans too are contending power and superpower systems, some of them so successful as to threaten to outrun their supplies of reductants, the foods or fuels on which their survival depends. It happens that one of the great superpowers has been established on the principle that contending powers can achieve a balance voluntarily. Surely the last best hope of earth is that humanity will agree to establish a power balance over the whole planet voluntarily. Assuredly, unless human reason contrives such a balance intelligently and deliberately, the inexorable biochemistry of power will achieve it for us stupidly and blindly. That message seems to be implicit in our own laryngeal marker of energy flow – the latest development in the still unfolding story of energy and the larynx.

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ACUTE LARYNGEAL OBSTRUCTION IN CHILDREN

A FIFTY-YEAR REVIEW

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When dealing with acute laryngeal obstruction, the first important consideration is the differential diagnosis of the cause. The author considers the following six types: acute laryngotracheobronchitis, acute epiglottitis, diphtheria, supraglottic allergic edema (angioedema), subglottic allergic edema (spasmodic croup) and foreign body in the larynx or trachea. He traces the development of the treatments that have in 50 years lowered the mortality rate from 70% to practically zero. High humidity, best supplied by an ultrasonic nebulizer, antibiotics, and corticosteroids in very high dose have been the prime effective measures. There still is controversy about the choice between tracheostomy and nasotracheal intubation if medical therapy is delayed or ineffective. The primary physician must know when and where to send these children in order to prevent the fatalities so frequent in previous years.

This is a progress report. I can outline only briefly the methods that have in 50 years reduced the mortality rate from about 70% to nearly zero.

Most of the contributions have been made by laryngologists. This is not surprising. A man who can see the larynx and has studied its diseases has a better grasp of the problems.

"Croup" is a symptom, not a diagnosis. Fifty years ago it was used as the diagnostic label for half a dozen potentially lethal conditions. In 1950 I[1] suggested using the term "acute obstructive laryngitis" to replace the word "croup" and advocated the following table of differential diagnosis (Table 1).

ACUTE LARYNGOTRACHEOBRONCHITIS

First I shall give a brief account of the evolution of the treatment of acute laryngotracheobronchitis, referred to hereafter as LTB.

In 1928 Baum,[2] who was the first to use this diagnostic term, described his experience with 24 cases, 10 of which ended fatally. He gave a good description of the clinical picture, including the subglottic swelling and the dry crusts which formed first in this area. He described the thick, sticky, gluelike secretion which forms in the trachea and bronchi following tracheotomy. He said, "A tendency to obstruction from plug formation was relieved in three of my cases by substitution of an O'Dwyer intubation tube for a tracheal cannula. I have, therefore, been led to the conclusion that tracheotomy has a tendency to cause too rapid evaporation of secretions, increasing the difficulty of expulsion and prolonging the period of dryness."[2] His conclusion was that intubation should be resorted to as soon as possible in all patients showing evidence of laryngeal obstruction, followed later by tracheotomy if it was necessary to retain the tube longer than three weeks. Baum had not yet read Proetz'[3] statements that cilia die if dry and that a jet of air directed at one spot rapidly destroys the ciliated epithelium. Nor had he read the Hildings' paper[4] describing the poor resistance of ciliated epithelium to mechanical trauma.

Humidification then was limited to steam in the room, but Baum was not impressed by its value. Baum advocated the use of immune blood transfu-

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TABLE 1. COMMON CAUSES OF ACUTE OBSTRUCTIVE LARYNGITIS IN CHILDREN

1. Acute laryngotracheobronchitis (subglottic laryngitis) (nondiphtheritic croup)
2. Acute epiglottitis (acute supraglottic edematous laryngitis) (influenzal laryngitis) (edema of the glottis)
3. Laryngeal diphtheria (membranous croup) (diphtheritic croup) (true croup)
4. Supraglottic allergic edema (angioedema)
5. Subglottic allergic edema (spasmodic croup) (spasmodic laryngitis) (false croup) (nocturnal croup)
6. Foreign body in the larynx or upper trachea

sions. Cultures from the intratracheal pus in most of his cases showed either a streptococcus or *Staphylococcus hemolyticus* or both. The latter has a well-known necrotizing effect.

Richards[5] in 1933 advocated direct laryngoscopy for diagnosis. He pointed out that usually the supraglottic tissues are not swollen, but that the subglottic tissues are intensely red and swollen and covered by crusts which can be removed with an aspirator, producing temporary relief. Very quickly crusts reform in the trachea and major bronchi. He was the first to describe the descending nature of the infection. All five of his tracheotomized patients died despite repeated bronchoscopic removal of crusts. Four patients intubated with O'Dwyer tubes lived. Postmortem examination showed necrosis of the epithelium of the trachea and major bronchi. A streptococcus was the predominating organism.

In 1936 the Jacksons[6] described essentially the same clinical picture recounted by Baum and Richards and pointed out that most of the fatal cases were registered in vital statistics as bronchopneumonia or pneumonia. Almost all of their cases were thought due to a streptococcal infection, but they suggested that filtrable agents (viruses) could be a contributing factor. The treatment they advocated was humidified air, parenteral fluids, early tracheotomy rather than intubation and bronchoscopic removal of crusts when they developed. They also said that "transfusion is one of the most powerful remedies in acute laryngotracheobronchitis." I also found transfusion of fresh whole blood to be very effective in the days before we had antibiotics. Transfusion of fresh whole blood supplies opsonins, complement, and antibodies; the factors needed to combat infection.

Holinger[7] in 1937 described the diffuse acute cellular infiltration of the conus elasticus. Postmortem examinations showed that the tracheobronchial epithelium was necrotic and was replaced to a large degree by fibrinous exudate. Holinger also advocated tracheotomy rather than intubation.

In 1938 Brennemann et al,[8] in a comprehensive paper, summarized the literature up to that time. Their mortality rate for the nine years preceding 1936 was 50%. After Holinger joined their staff in 1936, the mortality rate dropped to 25%.

Galloway[9] in 1939 was the first to advocate postural irrigation and drainage following tracheotomy. This method greatly reduced the number of bronchoscopic procedures necessary for removal of crusts.

The other lifesaving factor was Galloway's personal visits every few hours day and night. The average mortality rate reported by the Jacksons in 1936 was 70%. Galloway had only a 20% mortality in ten severe cases.

In 1940 I[10] was able to report 17 cases with only two deaths. I[11] advocated the use of a well-humidified oxygen tent, parenteral fluids, early tracheotomy, sulfanilamide drugs, transfusion of fresh whole blood and persistent personal attention to each patient.

Orton et al[12] in 1941 advised the use of O'Dwyer tubes followed by tracheotomy except for epiglottitis which required immediate tracheotomy. Orton was one of the first to use smears as well as cultures to determine the bacterial flora. He found staphylococci, streptococci or pneumococci in the endotracheal exudate. He thought sulfonamide drugs were helpful. His postmortem examinations showed ulceration and necrosis of the conus elasticus mucosa and leukocytic infiltration of the submucosa.

Gittins[13] in his 1942 paper presented to this Association was the first to stress differential diagnosis. I agree with his classification of infections, traumatic and allergic types, but he used the term "spasmodic croup" for those children which I think have subglottic allergic edema.

In 1942 McCaskey[14] recognized the damaging effect of catheter aspiration on the ciliated epithelium and advised placing a collar of adhesive around the catheter so that it could be introduced no deeper than one fourth inch beyond the lower end of the tracheal cannula. Deep aspiration was to be done only by the physician.

In his fifth paper presented in 1945 Baum[15] postulated what many now accept to be the etiology: a primary viral infection with secondary bacterial invasion.

He advised use of sulfonamide drugs, penicillin, transfusion of immune whole blood and use of humidified oxygen tents as medical measures. When obstruction was severe he believed that O'Dwyer tubes should be tried before tracheotomy.

In 1948 I[16] was able to report 52 consecutive cases, 15 of which required tracheotomy, with no deaths. The first 28 received sulfadiazine and the last 24 penicillin. Those receiving penicillin recovered more quickly. This experience convinced me that it is the secondary bacterial infection and *not* the primary virus that leads to serious complications.

I attributed the absence of mortality in this series to:

1. Careful personal attention to each patient.
2. Use of a humidified oxygen tent.
3. Adequate doses of penicillin.
4. Avoidance of instrumental trauma.
5. Postural irrigation and drainage.
6. Early tracheotomy.
7. Transfusion when indicated.

In 1948 Rabe[17] reported a study of 347 cases of "infectious croup" seen in a ten-year period. Careful bacteriologic cultures were made. He divided the cases into three etiologic categories: diphtheritic croup, *H. influenzae* type B croup and "virus" croup. Eight percent of the 347 cases had epiglottitis. The overall mortality rate for all types was 18%.

Rabe apparently did not recognize the importance of secondary bacterial infection in his cases of "virus" croup. Five of the eight fatal cases of "virus" croup had postmorten examination which showed laryngotracheopneumonitis.

In his 1957 paper Rabe[18] did advise penicillin and streptomycin prophylactically against possible secondary bacterial invaders in "non-bacterial" croup.

Synergism between viruses and bacteria has been known for a long time. Makowiak[19] in 1978 described four basic types of microbial synergism.

Neffson's[20] book, titled *Acute Laryngotracheobronchitis*, published in 1949, the only hard-cover text on this subject, *was* and *is* a valuable source of information and includes a most extensive bibliography. Neffson recognized the role of secondary bacterial infection, often mixed, and treated his patients accordingly. He favored the use of O'Dwyer tubes for LTB and tracheotomy for epiglottitis.

In 1959 I[21] reported 140 cases of LTB treated during a 14-year period with only one death. Tracheotomy was required in 28 cases. Six of the 13 more serious cases treated in 1958 received large IM or IV doses of corticosteroids. In all six there was rapid and spectacular improvement in the airway with marked reduction in the temperature within 12 to 24 hours. It seemed evident that parenteral administration of corticosteroids in *large dose* does reduce the incidence of tracheotomy.

Mills[22] says that hydrocortisone succinate given IM will produce a maximum plasma cortisol level in one-half to two hours.

In 1962 Fearon[23] reported 4,070 cases of LTB, 282 of which required tracheotomy. The mortality rate was less than 0.1%. This is an unsurpassed record and good evidence that skillful tracheotomy is a safe procedure. His preference for the term supraglottitis is justified because "epiglottitis" may involve predominately the other supraglottic structures.

In 1967 I[24] reported that in the preceding two years we treated 114 cases of LTB. Eighty percent of these, the more severe cases, received hydrocortisone IM injections. There were no tracheotomies and no deaths; rather definite proof of the effectiveness of steroids in reducing the incidence of tracheotomy.

Pennington[25] wrote in 1964, "In six years of practice in a large municipal hospital where approximately 200 cases of 'croup' are admitted each year, no tracheostomy has been necessary for an inflammatory laryngeal condition since the introduction of steroids in the treatment of edema of the subglottic compartment."

In 1967 Lederer et al[26] reported, "In allergic patients corticosteroids are particularly helpful since LTB in these patients tends to be more progressive and severe. Often one cannot immediately determine which of these patients are allergic. During an emergency, therefore, steroids might well be given *in all cases of LTB* having respiratory obstruction."

Ross[27] in 1969 reviewed 263 cases of LTB. In this series *no* tracheotomies were required for those children who received *adequate* doses of corticosteroids.

In 1971 Szpunar et al[28] in Poland used the adjective "fibrinous" to describe the most serious cases of LTB. I think fibrinous is a good word to describe those cases with secondary bacterial infection. They advised use of potent broad spectrum antibiotics in maximal doses. They also reported dramatic improvement after the first IV injection of a corticosteroid.

Adair et al[29] in 1971 advocated treatment of all cases of LTB with racemic epinephrine by intermittent positive pressure breathing (IPPB). They reported 237 cases admitted during a five-year period with 173 treated by IPPB, none of which required tracheostomy. Many others were treated as outpatients and sent home. I suspect some of these patients had subglottic allergic edema. Certainly none had the severe fibrinous type of disease described by Szpunar, Orton and others.

Four years ago Schuller and Birck[30] concluded that nastotracheal intubation is safer than pediatric tracheostomy. Their study was based on the treatment of 815 cases of LTB and 55 cases of epiglottitis. Six and a half percent of the LTB and 60% of the epiglottitis, a total of 86 patients, were intubated. The incidence of reversible complications was 7%. The incidence of delayed irreversible complications was 1.6%. Fifty-two of the "croup" patients were treated with racemic epinephrine by IPPB with a failure rate of 21%, and these cases required intubation. Steroids and antibiotics were used. General anesthesia, usually with a relaxant, was used for intubation. Intubation was possible in every case but 5% of these later required tracheostomy. There was no mortality associated with intubation in 86 patients.

In 1967 Striker et al[31] reported using nasotracheal intubation for 14 children who had acute LTB. Cardiac arrest occurred in five and two died. Four of the children developed subglottic stenosis. It was this experience that led them to discontinue nasotracheal intubation for children having "croup."

The choice of treatment method should depend on the skill and devotion of the available staff and on the type and severity of the disease. The real objective is to have a live child with no permanent disability.

In 1972 Fearon[32] reported 4459 cases of LTB with only two deaths. This extensive experience lends weight to his statement, "In the type of disease we have dealt with personally we find it difficult enough to force even a small bronchoscope through the *indurated* swelling in the subglottic space or through the swelling of the supraglottic area, let alone a flexible endotracheal tube."

In 1971 I[33] reported 418 cases of LTB with only one death in 1948. We began using hydrocortisone in large dose, 100 to 200 mg IM, in 1958. Since that time 80%, the severe cases, have received hydrocortisone and there have been no deaths. Only an occasional stat. tracheotomy has been necessary for those having severe obstruction on admission.

In 1971 I sent out a questionnaire to obtain other men's opinions of the value of corticosteroids in the treatment of LTB. In 44 replies based on 599 cases observed, 35 men said steroids reduced the incidence of tracheotomy and none reported any adverse effects. Some were using only one-fourth the size of the dose I had advocated.

The medical treatments of LTB advised by Gross[34] in 1977 were steroids in very high dosage IV, racemic epinephrine by IPPB, ampicillin, humidification and oxygen. If the airway is not adequately improved in three hours, his policy is to use nasotracheal intubation for children less than five years old and tracheotomy for those over five. If the nasotracheal tube cannot be dispensed with in 72 hours, he advised tracheostomy. Gross lists the good and the bad effects of establishing an airway by each method.

EPIGLOTTITIS

Epiglottitis was seldom recognized as a distinct clinical entity until the early 1940s.

Sinclair[35] in 1941 described ten typical cases having blood cultures positive for *H. influenzae* type B. The six patients who had both a sulfa drug and tracheotomy recovered.

Miller[36] gave the first comprehensive paper on epiglottitis in 1948. He described the clinical picture with which we are all now familiar. His treatment program included type specific rabbit antiserum, streptomycin, sulfadiazine and, when necessary, early tracheotomy after inserting a small bronchoscope. In many cases tracheotomy was necessary within four hours after the first symptoms.

His extensive bibliography includes earlier papers describing acute epiglottitis, but with different terminology.

I agree with Fearon's[37] 1968 statement that a general anesthetic should not be administered for acute obstructive supraglottic laryngitis until the airway obstruction is relieved by passage of a bronchoscope.

Extubation was not a problem in his 497 patients needing tracheostomy for either supra- or subglottic obstruction.

The only really controversial question about the treatment of supraglottitis is nasotracheal intubation vs tracheostomy.

In 1971 McGovern et al[38] wrote a paper titled "The Hazards of Endotracheal Intubation." They concluded that the hazards of tracheostomy are greater than those of endotracheal intubation, *but* few of their patients were children who had infection in the upper respiratory tract.

Baxter[39] in 1967 reported 103 cases of epiglottitis, 100 of which required tracheostomy and there was only one death. It remains to be seen whether this spectacular record can be matched by the advocates of nasotracheal intubation.

In 1971 I sent a questionnaire regarding the value of corticosteroids in treatment of epiglottitis to experienced endoscopists. There were 44 answers from men who had treated a total of 457 cases. Thirty used steroids and 27 said steroids reduced the incidence of tracheostomy. No one had seen any adverse reactions to the steroids.

In 1974 Strome and Jaffe[40] reported 12 cases of epiglottitis. In eight cases large doses of corticosteroids IV plus ampicillin improved the airway within two hours. Two required tracheostomy prior to use of steroids. Two were given steroids *after* intubation and were successfully extubated in less than three hours. This is convincing data showing that steroids decrease the edema and improve the airway.

Scheidemandel and Page,[41] discussing epiglottitis in 1975, state that a review of the world literature reveals numerous cases in which intubation was unsuccessful even when done by experienced people. The lowest mortality rates are reported by those who do early tracheostomy after inserting a bronchoscope. I wish there were more people who knew how to introduce a 3½ mm bronchoscope without general anesthesia and use of a relaxant.

LARYNGEAL DIPHTHERIA

I have not seen a case of diphtheria for years but it should be mentioned.

As Lang[42] said in 1965, "Diphtheria is still endemic in certain areas of the United States and in these areas physicians should be aware of the necessity for early diagnosis and treatment". Lang said that maintenance of an adequate airway is best obtained by tracheotomy. The medical treatment can be found in any standard textbook.

SUPRAGLOTTIC ALLERGIC EDEMA

Allergic edema involving the supraglottic structures can develop with great rapidity and present exactly the same clinical picture as that caused by epiglottitis. Direct laryngoscopy shows pale, watery edema of the epiglottis and aryepiglottic folds in contrast to the fiery red edema seen when the obstruction is due to bacterial infection. Allergic edema usually responds quickly to subcutaneous administration of 0.2 ml of epinephrine plus 100 mg of hydrocortisone phosphate IM or IV

Hansel,[43] in his 1953 textbook, gives a good description of supraglottic angioedema and states that it may be due to hypersensitivity to drugs, foods, inhalants or horse serum.

SUBGLOTTIC ALLERGIC EDEMA (SPASMODIC CROUP)

The term "subglottic allergic edema" is suggested for this malady because it is descriptive of both the anatomic location and the etiology. It is distinguished from other forms of obstructive laryngitis by its sudden onset, by the absence of fever and by the complete or almost complete remission of symptoms during the day. All primary physicians in our area who have used epinephrine for treatment of nocturnal "spasmodic croup" have reported that it is effective and said in addition that the early use of diphenhydramine hydrochloride as elixir of Benadryl® gives quick relief.

If the symptoms of so-called nocturnal spasmodic croup have not decreased in 12 hours, the child probably has infectious laryngotracheitis and treatment with corticosteroids and antibiotics should be started immediately.

For generations this clinical picture has been referred to as spasmodic croup, the inference being that the obstruction is due to adductor spasm of the vocal cords. This concept is erroneous: the sound of the croupy cough is identical with that produced by the subglottic swelling seen by direct laryngoscopy in cases of acute laryngotracheitis. In patients with "nocturnal croup," direct laryngoscopy shows a pale, watery edema of the subglottic tissues on each lateral wall.

Allergic symptoms are usually much worse at night, especially bronchial asthma.

Mills[22] points out that the plasma cortisol level is not constant throughout the 24 hours. The lowest values are found between midnight and 4 AM. This diurnal variation may well explain the occurrence of so-called nocturnal croup (subglottic allergic edema, spasmodic croup, false croup).

Croup has been referred to as a manifestation of allergy by many physicians who are experienced in dealing with allergic children. Some of these are Vaughn and Black,[44] Rowe,[45] Cohen[46] and Spain.[47]

Wolf,[48] a pediatric allergist, in 1966 discussed 48 cases of spasmodic croup and LTB. Forty-one of the 48 patients had signs and symptoms of allergy *prior* to their first attack of croup or LTB. Two non-allergic patients required tracheostomy. Most patients responded dramatically to the antiallergic drugs; epinephrine, ephedrine, aminophylline, theophylline and antihistaminics.

FOREIGN BODY IN THE LARYNX OR UPPER TRACHEA

The Jacksons'[49] superb 1936 textbook, *Diseases of the Air and Food Passages of Foreign Body Origin,* covers this subject so well that I can add nothing except a plea to train young laryngologists in the Jackson method of open tube endoscopy without anesthesia.

CONCLUSIONS

Primary physicians must be taught when and where to send these children with acute laryngeal obstruction.

Reading, both the old and the new, is an essential part of continuing education.

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DIAGNOSIS AND TREATMENT OF CAROTID BODY TUMORS

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The diagnosis and management of carotid body tumors are discussed, including the importance of good arteriography which allows visualization of all major feeding vessels. These include the carotid bulb, internal and external carotid arteries and the often neglected but important vertebral and ascending cervical arteries. Emphasis is placed on the importance of establishing tourniquet control of the common, internal and external carotid arteries. Surgeons removing carotid body tumors should be experienced in arterial wall repair by means of vascular shunts, end-to-end arterial anastomosis, and vein graft replacement of a segment of arterial wall.

Few unusual tumors have been discussed more in the literature than the carotid body tumor. Prior to the routine use of arteriography, the diagnosis of carotid body tumors was not always entertained and many surgeons were unexpectedly confronted with serious complications during exploration. Removal of these tumors may be very simple or an experience in control of hemostasis long remembered. Such an event occurred to one of this hospital's inexperienced surgical residents, who independently attempted to hasten the diagnosis of a small neck mass by performing a biopsy in the emergency room. This action necessitated taking the patient directly to the operating room to control the bleeding from the tumor. This article is presented to share the authors' experience in over two dozen cases performed in several hospitals during the last 15 years.

Carotid body tumors arise from the paraganglion cells of the carotid body, which is located bilaterally at or near the bifurcation of the common carotid artery. The carotid body is also composed of chemoreceptor cells which respond to decrease in oxygen tension by producing catecholamines, epinephrine and norepinephrine, causing increase in respiratory rate and depth with concomitant rise in pulse and blood pressure.[1,2] Because these tumors appear to arise primarily from the paraganglion cells (derived embryologically from the neural crest), the name paraganglioma is more appropriate than the frequently used term chemodectoma.[3] The term nonchromaffin paraganglioma best describes most of these tumors since they are histologically composed of cells derived from sympathoblasts rather than chromaffinoblasts, the two cell types differentiated from the neural crest ectoderm sympathogonia.[4,5] In a few reported cases, symptoms suggest that some tumors have functional components derived from the chromaffinoblasts.[6,7] Neurosecretory granules have been identified, by means of transmission electron microscopy, in normal chemoreceptor tissue and in carotid body tumors.[5,8] Furthermore, the presence of norepinephrine, epinephrine and serotonin has been demonstrated in both tissues by cytochemical techniques.[9]

In addition to the carotid body a number of other chemoreceptor centers are located in the head and neck area that can undergo neoplasia. These receptor centers and paraganglionic tumors are located or may be present in the jugular bulb, middle ear, base of the

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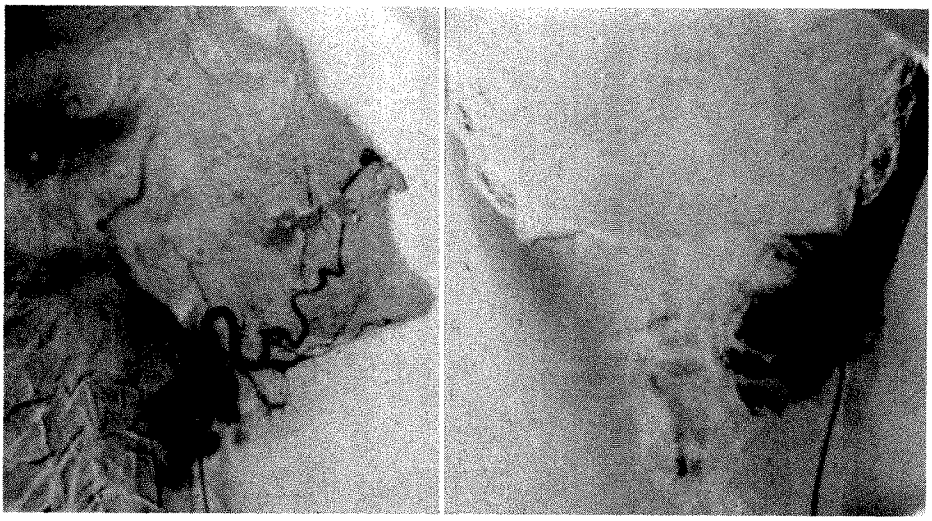

Fig. 1. Composite lateral (left) and AP (right) views of external carotid arteriogram showing classic tumor stain with distortion of the bifurcation and demonstrating vascularity supplied by external carotid.

skull, and lateral pterygoid, vagal, carotid bulb and aortic areas.

Tumors of the carotid body are usually benign, firm, rubbery, slow-growing masses presenting in the upper central neck area. The absence of pain and discomfort until the masses are of considerable size probably contributes to the long delay in the patient's seeking treatment. The tumors occur at any age but are most frequently diagnosed between the third and sixth decades. There is no apparent sex predilection. A familial tendency may exist but the genetic pattern has not been determined.[10-12] Carotid body tumors quite frequently occur bilaterally and are often associated with paragangliomas of the other chemoreceptor structures of the head and neck previously mentioned.[10]

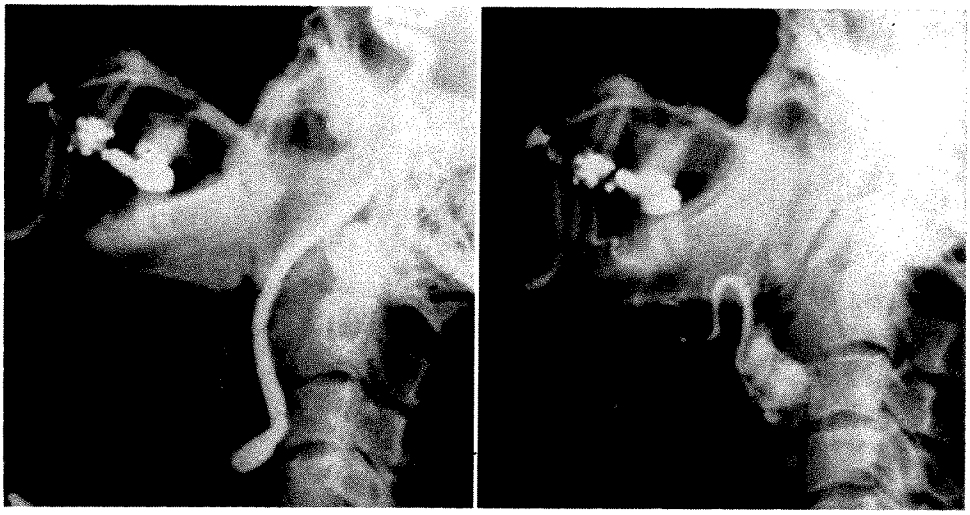

Fig. 2 Composite early (left) and delayed (right) phases of the internal carotid arteriograms demonstrating the blood supply and delayed staining of tumor by contrast dye from the internal carotid.

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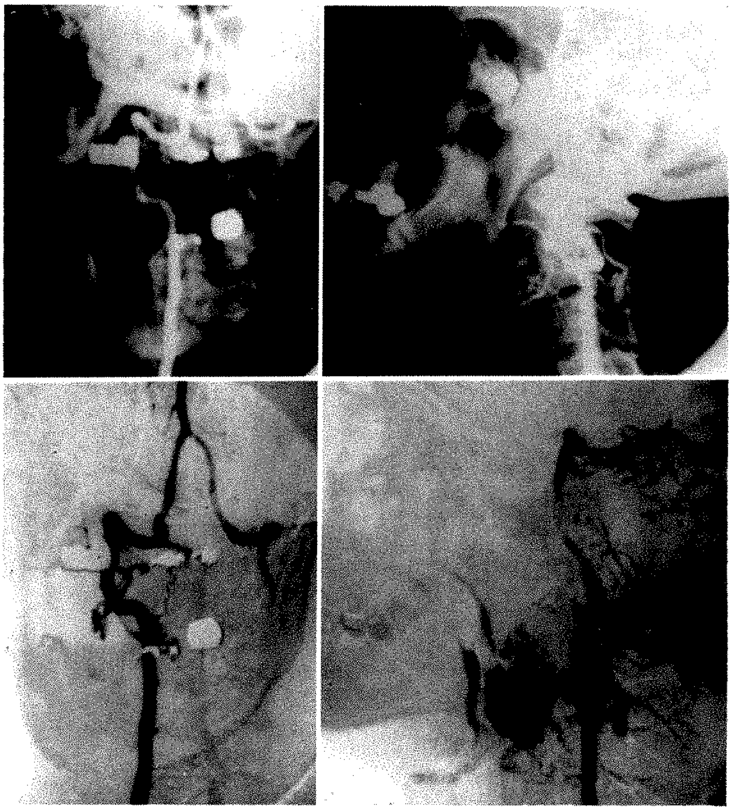

Fig. 3. Composite AP (left) and lateral (right) vertebral arteriograms (above) and subtraction studies (below) showing delayed tumor staining due to the supply of blood from the vertebral artery.

A patient reported by Katz[11] had ten siblings with carotid body tumors; three of them had bilateral disease.

The presence of a slow-growing, asymptomatic mass in the carotid triangle or upper neck should always elicit consideration of carotid body tumor as a diagnostic possibility. Other differential diagnostic possibilities include branchial cleft cyst, neurogenic tumor of the vagus or other cranial nerves, nodal metastasis, lymphoma, aneurysm or arteriovenous malformation. Specific physical findings of diagnostic assistance are: compressibility of the mass, a bruit, a similar mass on the contralateral side, other paragangliomas, or mobility of the mass in an anterior-posterior direction with limited mobility in a cephalic or caudal direction. Incisional biopsy of the mass is not warranted in most cases until the time of definitive surgery. Confirmation of the clinical diagnosis is provided by angiography. The presence of an eggshell-like mass widening the crotch of the bifurcation of the common carotid artery with displacement of the internal and external carotid arteries is pathopneumonic[13] (Fig. 1). These tumors initially derive their vascular supply from the vasa vasorum of the external and internal carotid arteries (Figs. 1 and 2). Very little has appeared in the literature concerning the additional blood supply from the vertebral and from the ascending cervical artery, a branch of the inferior thyroid artery which arises from the thyrocervical trunk (Figs. 3 and 4). Without injection of dye into these arteries major feeding vessels may be missed. The unsuspecting surgeon may be perplexed when tourniquets are applied to the common, internal and external carotid arteries and

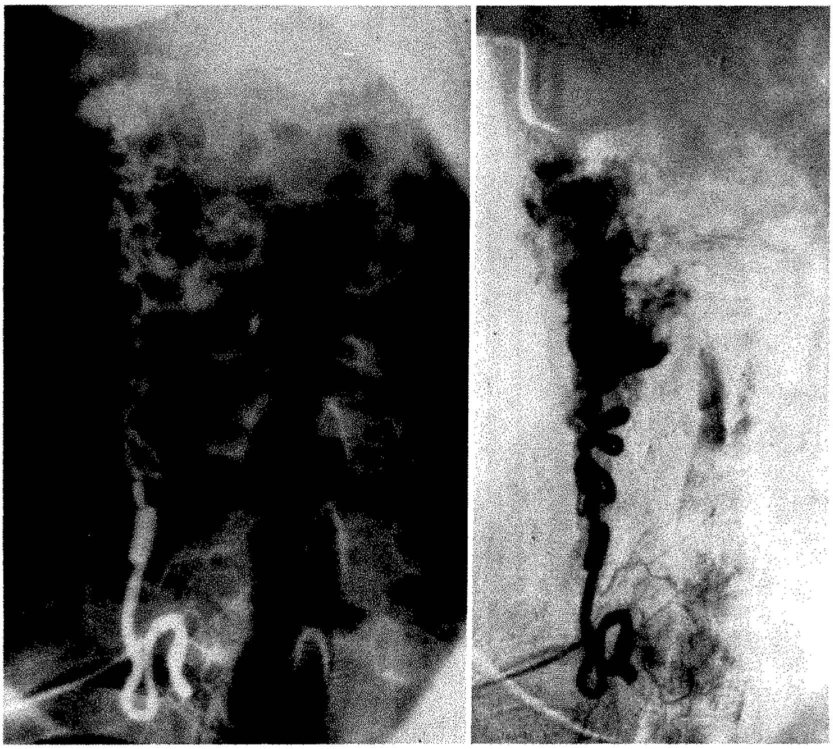

Fig. 4. Composite arteriogram (left) and subtraction study (right) showing dye in the thyrocervical trunk-inferior thyroid artery-ascending cervical arteries. The tumor blush demonstrates the supply of blood to the carotid body tumor from this vessel.

vigorous bleeding still persists during removal of some carotid body tumors. Other exceptions to the rule of delaying biopsy may include patients in poor health who are not surgical candidates and those with extensive metastatic lymph node involvement in whom tumors are considered nonresectable and in whom a histological diagnosis is desired prior to administration of radiotherapy.

The cells of both benign and malignant carotid body tumors are morphologically similar to those of the normal carotid body. The tumors are composed of nests of small uniformly sized epithelial cells (Zellballen) with finely granular cytoplasm surrounded by vascular stroma (Fig. 5). As previously mentioned, argentaffin and chromaffin cells have been identified.[5,8,9]

The incidence of malignant neoplasia is under 10%.[2] Bestler and Toomey[14] reviewed the literature and found that of the more than 500 cases reported, only 6% were classified as malignant. Since minimal histological difference exists between benign and malignant carotid body tumors, the diagnosis rests upon the presence of invasive characteristics or nodal metastases. Care must be exercised in differentiating between multiple chemoreceptor tumors and metastases.

Since the tumors are considered radioresistant, surgical resection offers the only available means of eradication. Since the incidence of malignancy is low and the hazard to major vessels and important nerves is evident, resection is not mandatory, particularly if contraindicated by other health considerations. As late as 1957 no less an authority than Martin[15] advised against removal since his experience indicated a five to ten-year life expectancy without resection. Farr in 1976[3] reviewed the 30-year experience of 37 cases at the Mem-

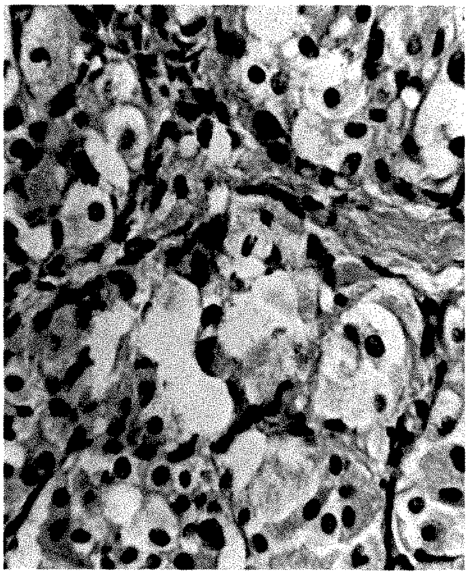

Fig. 5. Histological appearance of the nests of small epithelial cells (Zellballen) with intermeshed vascular spaces characteristic of carotid body tumors.

orial Hospital. Prior to 1945 the carotid bifurcation was resected in eight patients with a postoperative fatal hemiplegia occurring in four for a 50% mortality. Since that time the Memorial surgeons and others have adopted a more conservative approach, meticulously resecting the tumors and attempting to leave the arterial structures intact. From 1945 through 1967 this group operated upon 18 patients in whom arterial repairs were required: three perforations of the bulb were sutured with one postoperative hemorrhage resulting in death, and one end-to-end anastomosis was performed without event. Conley[16] feels there is indication for removing carotid body tumors under the following conditions: when the tumors are malignant and resectable; when they manifest aggressive growth characteristics regardless of histological diagnosis; when they are of small or medium size situated in the region of the carotid bifurcation in patients under 50; and when there is extension of the tumor into the pharynx and palate interfering with swallowing, breathing and speaking. Our experience in over two dozen cases utilizing improved techniques of vascular repair and grafting fully supports these concepts and makes resection more feasible.

The surgical technique is based upon several important anatomical facts. The carotid body tumor arises in the adventitia of the posterior medial surface of the common carotid artery extending cephalically to the bifurcation.[5] The adventitia thus provides a nice cleavage plane, allowing meticulous resection by cutting down, but not into, the wall of the arteries and more or less shelling out the arteries from the tumor. Because of its site of origin and growth pattern, the tumor usually encircles both internal and external carotid arteries with, lastly, involvement of their posterior lateral aspects. The incision of the tumor can thus most safely be carried out in the latter area. There is often a significant adherence to the wall of the bifurcation and bulb where the blood supply of the tumor arises from the vasa vasorum. When there is marked thinning of the arterial wall, perforation is sometimes an unavoidable hazard. Attempts at repair of the perforation when arteriosclerotic placques are present may result in further damage and actual disintegration of the bulb and artery. The high risk of perforation and the ever-present possibility of damage to the internal carotid, requiring shunting and end-to-end anastomosis or vascular grafting, mandate preoperative consideration and preparation for these complications.

After elevation of skin flaps, reflection of the anterior border of the sternocleidomastoid muscle, and opening of the carotid sheath, it is essential to loosely place controlling rubber tube-tape tourniquets above and below the tumor, around the upper portions of the internal and external carotids and below and around the common carotid artery. Identification and ligation of feeder vessels from the vertebral and ascending cervical vessels are also important. Silicone-coated polyethylene tubing of several diameters or prefabricated Javid internal-shunt catheter, Javid clamps, Derra clamps, Fogarty® clamps and Bulldog clamps should be in the instrument set-up (Fig. 6).

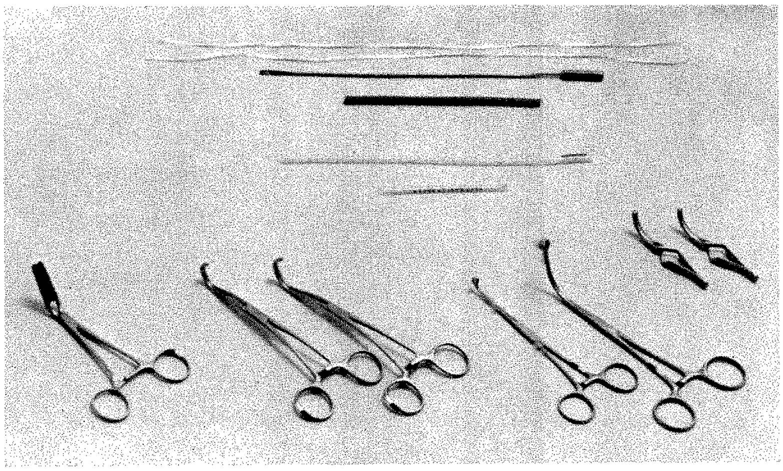

Fig. 6. Photograph showing Fogarty®, Derra, Javid and Bulldog vascular hemostats, tape-rubber tourniquets, and silicone internal shunt catheters.

In the event of a perforation, Satinsky or Derra hemostats are applied and the perforation repaired with 5-0 or 6-0 vascular silk or other permanent sutures (Fig. 7). If the artery is more severely damaged, a shunt can be inserted through an arteriotomy or through the damaged area, and by application of the tourniquets, hemostasis is achieved while the internal carotid is continuously perfused (Fig. 8). The external carotid is usually resected with the tumor and the distal branches ligated. A small amount of heparin is injected into the common carotid artery to diminish thrombosis. In most cases (all in our experience) an end-to-end anastomosis can be achieved, but if necessary a segment of the jugular or saphenous vein can be obtained, placed over the shunt, and sutured into place.

When tumors are not resectable or after resection of malignant tumors, radiation may be considered. We have performed repeated metastatic node resections in one case. In younger patients in whom resection has been thorough, it may be better to withold radiation to

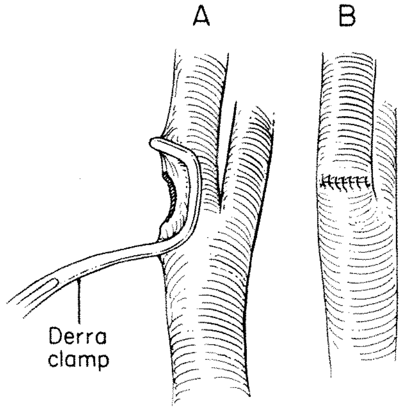

Fig. 7. Illustration demonstrating the technique of application of Derra clamp and repair of perforated vessel.

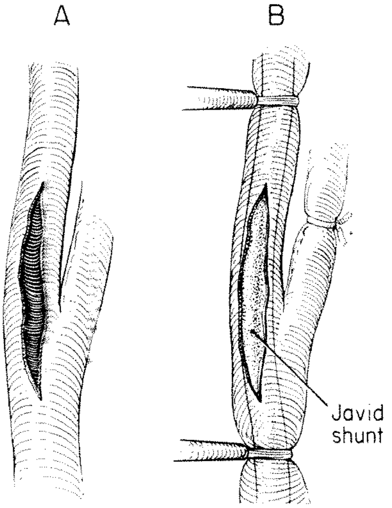

Fig. 8. Illustration of internal shunt in common and internal carotid arteries for continued perfusion of blood to the brain during vascular repair, end-to-end anastomosis or vein grafting.

facilitate repeated resections should they be required.

DISCUSSION

A carotid body tumor must always be considered in the differential diagnosis of a slowly growing mass in the upper middle neck that has limited vertical mobility. Arteriography has replaced the need for biopsy except when malignancy is suspected and if histological documentation is necessary prior to administration of radiotherapy. During arteriography, it is important that contrast material be passed into the vertebral artery and thyrocervical trunk as well as the common, external and internal carotid arteries in order to reveal all major feeding vessels of the carotid body tumor. When an enlarged ascending cervical artery (a branch of the inferior thyroid artery) was first encountered by the senior author during surgery, it was considered to be an anomalous vessel and was divided and ligated. A failure of arteriography to demonstrate, or of the surgeon to recognize, the blood supplied by arteries other than the internal and external carotid arteries may result in sufficiently uncontrolled bleeding to provide a memorable experience.

Judicious clinical judgment is necessary for proper selection of the course of action. The options include surgical removal, radiation or observation. Surgical excision is indicated in younger patients and in most patients who are in good health with a life expectancy of eight to ten or more years. Health permitting, small tumors should be removed before they encircle the major vessels and complicate surgery. Large tumors, producing symptoms such as cranial nerve palsies and difficulty in swallowing, speaking and breathing because of intraoral extension, should be excised.

The surgeon undertaking removal of any carotid body tumor must be prepared to control massive hemorrhage and have experience in vascular repair, end-to-end anastomosis and, if necessary, vein graft replacement of a segment of the internal and carotid arteries. The high morbidity and mortality rate contraindicates simple ligation of these vessels as a routine method for controlling hemorrhage during tumor removal. The surgical instrument set-up for carotid body removal should include vascular hemostats, tourniquets and catheter shunts in anticipation of major vessel hemorrhage.

The numerous articles reporting cases of massive hemorrhage and severe morbidity, hemiparesis and death when ligation of the common and internal carotid arteries is performed indicate a relatively high incidence of vascular damage during carotid body tumor removal. Meticulous dissection after cutting through the tumor to the vessel adventitia has diminished the frequency of severe vessel injury. Extensive adhesiveness to and thinning of the vessel wall by the tumor frequently (in approximately one third of cases) require suture repair. When the thinned vessel wall also contains numerous arteriosclerotic plaques, distintegration of the carotid bulb can occur with application of the vascular hemostats. This was experienced in four cases (approximately one sixth) of our series and a similar incidence was reported by Farr.[6] The necessity of early tourniquet control of the common, internal and external carotid (or its branches) is evident.

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GUIDELINES OF GRANTS
TRUSTEES OF AMERICAN OTOLOGIC SOCIETY

A matter of continual concern to the members of the Board of Trustees of the American Otological Society is the determination of guidelines for the making of grants from its research fund. The following is our current formulation of policy.

Our objective is clearly before us as the problem of otosclerosis: its diagnosis and management, the possible causes and underlying conditions (such as the hereditary background), and an understanding of the disorder that may lead eventually to its prevention and cure.

Our present lack of understanding of the disorder and the absence, as far as known, of any similar condition in animals below man, make research in this field particularly difficult. A direct attack on the disease is hardly feasible; therefore it seems to be sound strategy to try circuitous approaches, such as the investigation of bone development, growth, and repair under various conditions, and the study of other diseases that show suggestive correspondence. It is possible that directions of investigation that may seem initially somewhat remote from otosclerosis itself may provide insights that will eventually lead to success in reaching our goal. The applicant should describe correlations between proposed research with the clinical pathological entity of otosclerosis.

Therefore, our policy is to aid and encourage research in the immediate field of otosclerosis and also in adjoining fields if in our considered opinion there is a substantial promise that the results obtained will be of assistance in the ways just indicated, and may lead to the attainment of our objective.

To stimulate the attainment of this objective, the Board of Trustees wishes to remind the general otolaryngologic community that funds are still available for suitable grants. Application forms may be obtained from the office of the secretary of the Research Fund Trustees of the American Otologic Society.

The grant request should be submitted by January 31, 1979, to David A. Hilding, MD, Secretary, 1300 Tower Road, Winnetka, IL 60093. Telephone (312) 441-5023.

Ann Otol 87:1978

GLOMUS JUGULARE AND VAGALE

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The therapeutic results in 72 patients with glomus jugulare and nine with glomus vagale have indicated a surgical cure rate of 80% in the former and 100% in the latter. Radiotherapy demonstrated a 65% tumor response rate and a 25% cure rate histologically and clinically. Embolization with Gelfoam® beads in seven patients resulted in diminished tumor size and arterial circulation from the external carotid system. However, in all cases the tumor persisted. Embolization diminished intraoperative bleeding. Nevertheless, the use of embolization as a palliative modality demonstrated significant symptomatic relief in aged, debilitated patients and in all patients with large inoperable glomus jugulare tumors.

Glomus tumors or chemodectomas arise from the chemoreceptor system found along the jugular bulb, middle ear, vagus nerve and chest.[1-8] They are the most common neoplasms of the middle ear. Many aspects of this article have been previously published.[9-13] This paper updates our results. In addition, we will emphasize embolization[14] which can serve a useful purpose, in some cases, prior to resection and perhaps may be an adjunctive therapy for symptomatic relief in those tumors which are not resectable or in debilitated patients.

ANALYSIS OF CLINICAL POPULATION

Glomus tympanum tumor, common tumors originating in the middle ear, and carotid body tumors have been excluded from this series. In this study there are 72 glomus jugulare tumors and nine glomus vagale tumors. The male to female ratio is 6:1. The average age is 53 years with a range of 16-83 years. Average duration of symptoms prior to diagnosis is 13.1 months. The incidence of multiple tumors is 10%.

CLINICAL SIGNS AND SYMPTOMS

The majority of these cases had conductive hearing loss, pulsating tinnitus, or a mass behind the tympanic membrane (Tables 1 and 2). Neurologic deficits of the cranial nerves were common. Most often the VII nerve was paralyzed. Less often VIII (labyrinthine invasion), IX, X, XI, XII, or sympathetic nerve paralysis occurred (Table 3). Bleeding from the ear or a protruding polyp in the external auditory canal was present in about one third of the cases of glomus jugulare tumors (Table 1). A mass was palpated in the neck in seven of nine cases of glomus vagale tumors (Table 2).

Neurologic involvement of cranial nerves is of critical importance because these nerves may delineate routes and

TABLE 1. PRESENTING SIGNS AND SYMPTOMS IN 72 GLOMUS JUGULARE CASES

Signs and Symptoms	*No. of Patients*	*%*
Conductive loss	42	58
Tinnitus	40	56
Mass of external canal*	21	29
Bleeding	21	29
Mass behind TM	33	46
Aural discharge	21	29
Aural pain	22	31
Vertigo	15	21
Brown's sign	19	26
Mass in neck	5	7
Canal paresis	8	11
Decreasing vision	2	3
Cranial nerve palsy	27	38

*Fourteen cases treated initially elsewhere.

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Presented at the meeting of the American Laryngological Association, Palm Beach, Florida, April 22-23, 1978.

TABLE 2. PRESENTING SIGNS AND SYMPTOMS IN 9 GLOMUS VAGALE CASES

Signs and Symptoms	*No. of Patients*	*%*
Mass in neck	7	78
Pharyngeal mass	4	44
Pharyngeal pain	3	33
Sudden deafness	1	11
Black-out spells	1	11
Vertigo	1	11
Cranial nerve palsy	5	55

areas of the cancer's extension. There is cranial nerve involvement in 38% of glomus jugulare tumors and in 55% of glomus vagale tumors.

Glomus jugulare tumors located in the jugular bulb have ready access to various portions in the temporal bone and the foramina at the base of the skull, since these tumors spread along the lines of least resistance. Intracranial extension, therefore, can follow along the carotid artery, cranial nerve foramina, into the nasopharynx, intravascularly into the lateral sinus and inferior petrosal sinus, or follow the temporal bone air cell system to the petrous apex, retrofacially or via mastoid air cells.

The signs and symptoms of glomus vagale tumors are more difficult to diagnose and are less specific. The most predominant sign is a neck mass, high in the neck. The mass may be pulsatile and have a bruit. Ipsilateral paresis involving the IX and X nerves may be present in half of the cases. The XI and XII nerves are infrequently involved. Occasionally pharyngeal swelling may be evident in the tonsillar area and lateral oropharyngeal wall. The mass is not associated with pain or severe discomfort. Generally, the symptoms are referable to the parapharyngeal space.

NEURORADIOLOGIC EVALUATION

Plain x-rays of the skull and mastoid x-rays are the least useful tests and give minimal information on localization and growth patterns. Polytomes indicate 1) a general picture of the osteology, i.e., specific patterns of bone destruction, 2) areas of bone erosion, i.e., indicating direction of tumor growth, 3) a soft tissue mass in the middle ear with or without ossicular destruction, 4) invasion of cochlear or VII nerve (fallopian) canal. CAT scanning with or without contrast may give additional information with respect to CNS invasion.

Retrograde venous jugulography[11] indicates the inferior border of the tumor, intraluminal invasion or extraluminal compression of the jugular vein lumen or CNS invasion of the sigmoid sinus, lateral sinus, or inferior petrosal sinus.

The arteriogram distinguishes between various types of chemodectomas as well as other vascular tumors. It delineates the superior and inferior borders of the tumor. It indicates the blood supply of the tumor. CNS invasion is indicated by arteriography by means of two findings: visualization of direct tumor invasion of the CNS and observation of abnormal CNS vessels arising from the internal carotid artery to supply the tumor.

TABLE 3. CRANIAL NERVE PALSIES IN GLOMUS JUGULARE AND GLOMUS VAGALE TUMORS

Cranial Nerve Palsies	*No. of Glomus Vagale Patients*	*%*	*No. of Glomus Jugulare Patients*	*%*
Total incidence of palsies	5	55	27	38
VII	0	0	17	24
VIII (labyrinthine invasion)	1	11	3	4
IX	4	44	2	3
X	2	22	5	6
XI	1	11	2	3
XII	1	11	7	10
Horner's (sympathetics)	1	11	4	6

TABLE 4. THERAPEUTIC RESULTS*

	Surgery	*Radiation*	*Combined*
Glomus Jugulare	39/49 (80%)**	3/12 (25%)††	7/11 (64%)
Glomus Vagale	8/8 (100%)†	0/1 (0%)	0/0 (0%)

*Cure rate, 6.5 years NED.

**Three cases beaded, two not resected.

†One case beaded, completely resected.

††Three cases beaded, all persisted.

CLINICAL DETERMINANTS REGARDING SURGICAL INTERVENTION

Generally, extracranial tumors or those which arise posterior to the internal carotid artery are amenable to surgery. Consequently, such findings as paralysis of the V (always sensory) or VI (Dorello's canal) nerves, papilledema (initially ipsilateral), or hydrocephalus represent stages of glomus tumors which are not resectable.

Ipsilateral involvement of the IX, X, or XII nerves does not imply that the lesions are not resectable. However, tumor extension to the nasopharynx, the petrous apex or anteriorly along the carotid artery intracranially imply nonresectability. Posterior extension along the jugular vein or sigmoid sinus are resectable. Intracranial extension generally follows more than one pathway through the foramina of the base of the skull. This finding explains the frequent surgical failure rate.

TUMOR EMBOLIZATION

If the tumor is advanced or extensive, embolization of selected branches of the external carotid artery may temporarily decrease tumor vascularity and alleviate troublesome symptoms. Vascular embolization of glomus tumors with Gelfoam® beads is used as an adjunct to surgery or for palliation to control symptoms. This is accomplished by decreasing tumor swelling as its blood supply is diminished. Seven cases have been done in extensive lesions or in high-risk patients. In all cases, repeated carotid arteriograms three months to two years later indicated decreased tumor vasculature.

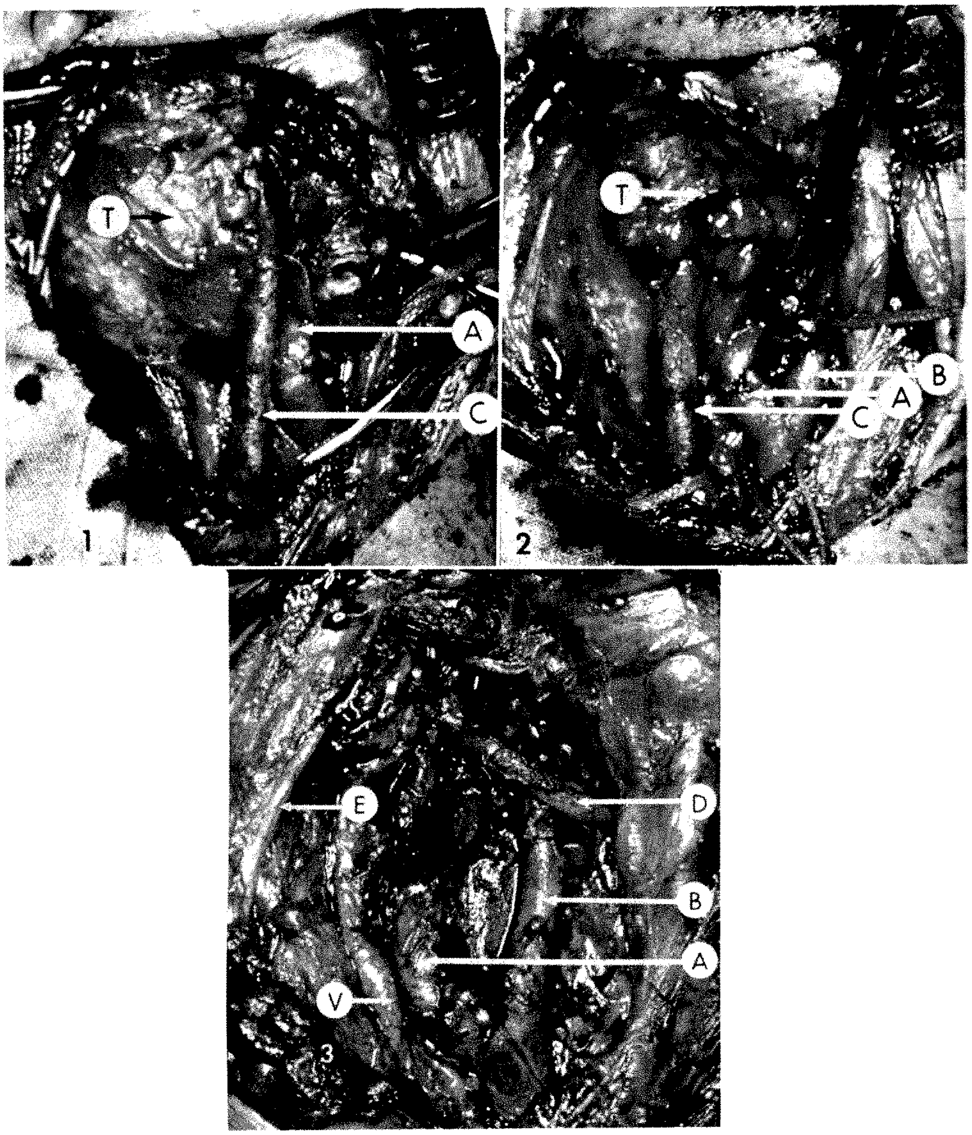
SURGICAL THERAPY

Surgery is the preferred treatment of choice (Table 4). About 80% of the glomus jugulare tumors and 90% of glomus vagale tumors are surgically resectable. Only 25% of glomus tumors are radiocurable. Because of the slow growth of the tumors and small metastatic rate, patients who are very old and debilitated are not operated upon. In most cases, these patients outlive their disease.

A combined radical mastoid, hypotympanic and neck resection is the standard procedure for glomus jugulare tumors that do not invade the central nervous system. The jugular vein is always taken with the resection whether the tumors invade the jugular vein lumen or extraluminally compress the vein.

It is advisable to approach the tumor from the neck (i.e., from below) by isolating and ligating the major feeding vessels from the external carotid artery. The ascending pharyngeal, posterior auricular, occipital, internal maxillary and feeding branches of the vertebral artery are usually involved. The cranial nerves are identified and preserved. The jugular vein is isolated but not tied initially. This is done to allow venous return of blood from the tumor to avoid swelling and congestion of the tumor with blood prior to resection. A standard radical mastoidectomy is then performed with facial nerve decompression and mobilization, if required. The sigmoid sinus is exposed, compressed and ligated. The lower end of the jugular vein is ligated below the level of tumor removal.

Resection of the glomus jugulare tumor is based on the inferior petrosal sinus, since it is not visible until the tumor is removed. This sinus lies medially to the tumor and may produce brisk bleeding that can only be controlled by compression. One must not press so hard



Figs. 1, 2, and 3. Resection of glomus vagale tumor. T - Tumor; D - Hypoglossal nerve; C - Internal jugular vein; B - Internal carotid artery; A - External carotid artery; E - XI nerve; F - Carotid artery; V - Vagus nerve.

as to deviate the brain stem and precipitate a respiratory or cardiac arrest. Temporal bone resection should not be employed. It is the wrong operation for this tumor since it would cut across the planes of tumor spread, leaving the tumor medial to the resected margin. A careful and meticulous otologic procedure is the treatment of choice.

Resection of glomus vagale tumors only requires a neck approach (Figs. 1, 2, and 3). However, a standard cervical approach may not be adequate for exposure of the base of the skull, of the jugular foramen, or to control the bleeding. Occasionally, removal of the transverse processes of cervical vetebrae, styloid process, or mandibular osteotomy may be needed for exposure.

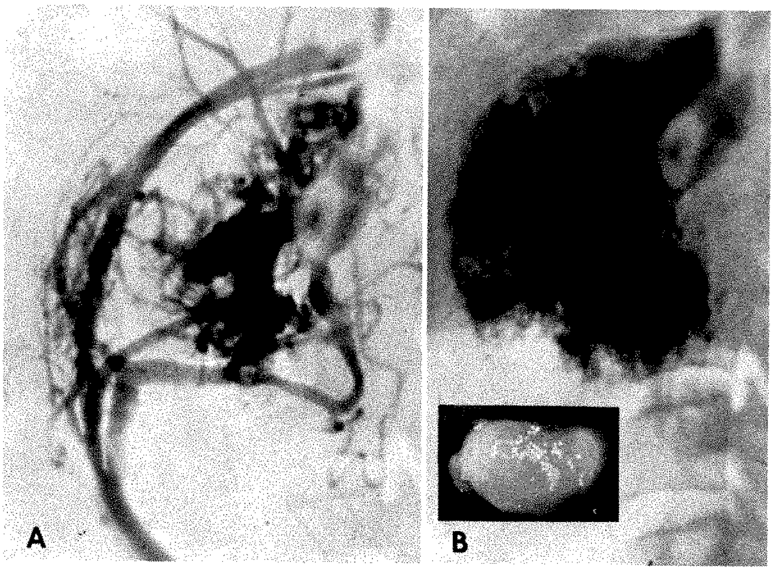


Fig. 4. A) Arteriogram (subtraction technique) demonstrating large glomus vagale tumor and displacing internal carotid artery anteriorly. B) Capillary phase of arteriogram. Note rich vasculature of tumor. C) X-ray photograph of resected tumor specimen which delineates beads in tumor; patient was beaded three days prior to surgery.

Branches from the external carotid artery supplying the intravagale portion of the tumor are ligated. These are generally identified from the preoperative arteriogram. It is necessary to identify and preserve the X, XI, and XII cranial nerves. Dissection usually follows the carotid sheath. Occasionally, the internal jugular vein may need to be sacrificed. Transection of the X nerve is usually not necessary. The blood supply from the vertebral artery is medial to the tumor and may need to be ligated after tumor removal.

Radiotherapy in doses from 4600-6000

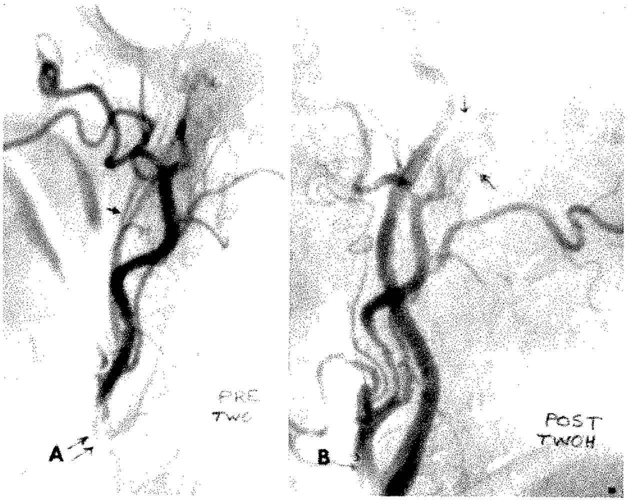


Fig. 5. A) Large glomus jugulare tumor (subtraction technique). Catheter in place (two arrows). Note tumor circulation from ascending pharyngeal artery (single arrow). B) Catheter in place in external carotid (two arrows). Blanched tumor vasculature and occlusion of ascending pharyngeal artery (single arrows).

rads yields a 65% tumor response rate (histologically) and a 25% "cure" rate clinically and by arteriography.

RESULTS

The therapeutic results are listed in Table 4. The best results were obtained by surgery. Preoperative radiation followed by surgery in glomus jugulare tumors may aid in resection of large tumors, i.e., 64% cure rate. However, if combined neurosurgical and mastoid-neck procedures are anticipated, radiation should not be used since there is a high risk of CSF leak and meningitis. Also, if fascia lata grafting of the dura is required, radiation cases will not heal adequately (we have had three deaths in the past). In the past six years, there have been no deaths from surgery with our present procedure.

The major problem in most instances can be divided into two factors, i.e., exposure and bleeding. The problems of exposure have been outlined above except for those unresectable lesions which lie anteriorly to the internal carotid artery. Bleeding is, therefore, a major issue. The transfusion range for these cases is 0-14 units of blood with an average of 4 units. One patient had a pulmonary embolism and another patient had respiratory arrest while the tumor was being removed from the inferior petrosal sinus. All patients survived the surgery and left the hospital in reasonably good condition. The major complications included persistance of tumor, and facial nerve palsy in seven patients.

In our series most of the lesions were large. The surgical cure rate for glomus jugulare tumors was 80% and glomus vagale 100%. For surgical failures, reoperation, radiation or embolization is employed. The latter procedure is usually of little longlasting benefit. Reoperation may occasionally be easier technically than the initial surgery if the lesion is devascularized. Recently, we have used embolization of the external carotid artery branches in order to control surgical bleeding or symptoms for inoperable lesions. Obviously, tumor vasculature from the CNS was not affected by this technique. However, arteriograms, even two years later, demonstrate a diminished arterial supply to the tumor from the external carotid system. Of the seven cases that were treated, one was resected successfully with no transfusion and six cases had persistent tumor in the CNS, i.e., in those areas where tumor beading was not attempted. On arteriography the latter six cases had diminished blood supply from the external carotid system. This technique may prove to be a valuable adjunct in the future.

DISCUSSION

Lussenhop and Spence[15] and Lussenhop et al[16] described the use of Silastic® artificial emboli in the treatment of cerebral arteriovenous malformations. They demonstrated that emboli are preferentially directed to the malformation, guided by two factors: 1) the larger caliber of the vessels feeding the malformation compared to those feeding the brain, and 2) the configuration of arterial branching, success being more likely to occur when the feeding arteries represent the continuation of the parent trunk. Newton and Adams[17] described embolization of a spinal angioma by injected lead pellets via a percutaneously introduced catheter as opposed to surgical arteriotomy utilized by other reports.[15,16,18]

Since then, percutaneous catheter embolization has become more popular[19,20] for treatment of cerebral and spinal arteriovenous malformations. It requires no surgical incision or general anesthesia, does not entail damage to the carotid or vertebral arteries and it permits direct clinical observation of the awake patient, an important guide during the procedure. Besides, the procedure can be repeated at a later date, if necessary, without sacrifice of an artery or reoperation through a previously scarred site.[20] Concomitantly, reports appeared describing the use of this technique in treatment of gastrointestinal hemorrhage,[21] intractable epistaxis,[22] as well as extracranial vascular neoplasms.[23]

Proximal ligation of the external carotid artery fails to produce an effective decrease in vascularity of the tumor fed by branches of this artery. This failure is the result of collateral flow through a multitude of anastomotic channels which connect these branches with those of other arteries in the neck such as the vertebral, the opposite external carotid, the ascending cervical and the deep cervical arteries. The "opening up" of such anastomotic channels has been demonstrated angiographically and has caused technical difficulties at reexploration.

Embolization aims at blocking the *vascular bed* of the tumor, causing thrombosis and preventing the establishment of collateral channels as long as obliteration of the vascular bed is maintained. This technique is used in four instances: 1) preoperative reduction of the mass of tumor and anticipating reduction of intraoperative bleeding, done in three cases of glomus jugulare and one glomus vagale tumor (Fig. 4 A, B, and C); 2) in patients who refuse surgery, one patient; 3) in massive tumors that extend intracranially and are not resectable, one patient (Fig. 5 A, B); or 4) in debilitated, aged patients who cannot tolerate the surgical procedure, one patient. In the third and fourth groups, we had two patients where selective embolization was performed with dramatic symptomatic improvement and significant reduction of tumor vasculature on repeated arteriography.

In a series of 27 cases of lesions extrinsic to the central nervous system treated with percutaneous embolization, Hilal and Michelsen[23] included eight case of glomus jugulare tumors. In five of these, embolization was performed as a preoperative procedure and resulted in complete excision without need for transfusion in three cases and permitted a wide partial resection in two cases. In two of the remaining three cases, embolization was the only therapeutic measure, and it resulted in disappearance of the symptoms in two cases (one of them was followed for five years). The last patient in the series was the only death in the entire experience of more than 100 patients.

We have had no major complications from embolization in our small series. However, there have been some reported by other neuroradiologists. One patient had a temporary Horner's syndrome as our only complication in this series. Theoretically, Gelfoam® beads can escape into the intracranial circulation via the backflow to give rise to central nervous system complications, i.e., CNS infarctions. For example, with occlusion of the external carotid artery by embolization there may be an increased backflow to the internal carotid artery. Emboli may escape from the external system to lodge in the internal carotid circulation and infarct the brain.

In another series of patients with nasopharyngeal angiofibromas, we have had, in one case out of 12, a transient CVA which cleared up in two hours. In another patient, emboli were detected in the middle cerebral artery, but the patient was asymptomatic.

Selective angiography of the external carotid artery is an indispensable prerequisite to embolization. The vessels feeding the tumor are identified. The catheter should be advanced as close as possible to the lesion before emboli are introduced. This will reduce the chances for reflux of emboli back into the carotid bifurcation where stray emboli may enter the internal carotid artery. This may be reduced further by the use of a double lumen balloon catheter.[23]

Radiopaque Silastic® spheres and Gelfoam® were most frequently used for embolization. Silastic® spheres (.5-4 mm in diameter) are impregnated with barium and are, therefore, radiopaque for visualization on radiographs. They require, however, a special, large diameter catheter which may be difficult to maneuver into various arterial branches. A 3 mm sphere requires a .110 inch inner diameter catheter.[20] Gelfoam®, on the other hand, may be cut in relatively large pieces which can be squeezed through the usual angiographic catheter. It may be mixed with tantalum powder, a radiopaque marker, to permit radiographic detection. Its most serious disadvantage is recanalization of the occluded vessels. This renders it suitable only for temporary preoperative embolization. Manelfe et al,[24] using the renal artery of the dog as the experimental model, studied the results of embolization by serial angiograms up to 30 days after the procedure. They demonstrated secondary recanalization in two out of three animals.

More recently, liquid Silastic®, an intravascular adhesive, has been developed in a low viscosity liquid form[23] which can be injected through a small double lumen catheter and will polymerize into a hard rubbery substance in 5-6 minutes producing permanent obliteration of the vascular bed of the tumor.

In conclusion, glomus jugulare and vagale tumors present a major problem for therapy. Recent refinements in diagnostic evaluation and treatment techniques have improved the therapuetic outcome.

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JUVENILE NASOPHARYNGEAL ANGIOFIBROMA

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The diagnosis of angiofibroma can be suspected in most cases by clinical examination, supplemented by routine x-rays and tomograms and is confirmed by angiography. Adjunctive therapy including embolization, estrogens, cryotherapy and arterial ligation is discussed. Surgical resection is the preferred treatment. Radiotherapy as the primary treatment modality is contraindicated except in select cases.

Juvenile nasopharyngeal angiofibroma, a histologically benign, but at times, a clinically malignant vascular tumor of adolescent males, continues to challenge the head and neck surgeon. The improved surgical curability of this lesion over the past 10 to 15 years has been primarily related to preoperative angiographic tumor assessment and the selection of surgical approaches dictated by the extent of the tumor. At the present time there remains controversy related to the following: diagnostic procedures, adjunctive surgical therapy and the role of radiotherapy in the treatment of these tumors. This presentation will be limited to these controversial areas.

DIAGNOSIS

The experienced pathologist is able to diagnose angiofibroma accurately, on biopsy, in practically all cases. There are no contraindications to biopsy, provided the surgeon recognizes that the lesion may bleed profusely. This usually requires nasal packing and, occasionally, transfusion. Anticipation of the diagnosis, therefore, requires biopsy in the operating room usually under general anesthesia. The alternative method to biopsy, for diagnosis, is arteriography. The arteriographic picture is diagnostic for angiofibroma. The arteriogram is also necessary to define the vascular supply and the extent of the tumor. The latter can be determined by computerized axial tomography (CAT) but, unfortunately, the blood supply to the tumor is not identified by this method. If arteriography is employed as a diagnostic method then occasionally patients presenting with nasopharyngeal masses which are not angiofibromas may undergo unnecessary arteriography.

In the present series of ten cases, three patients were biopsied for diagnosis. These three patients, clinically, had a preoperative diagnosis of angiofibroma. All patients required general anesthesia for biopsy and postoperative packing. One required a transfusion. Four patients with nasopharyngeal masses, suspected of being angiofibroma by the referring physician following physical examination, routine sinus x-rays, and tomograms were thought clinically to have lesions other than angiofibromas. These patients did not have arteriograms but underwent biopsy. The results were antrochoanal polyp in three patients and lymphoma in one patient. It is evident that with accurate clinical assessment supplemented by routine sinus x-rays and, at times, CAT scans and tomograms, the clinical diagnosis of angiofibroma is very accurate. The number of unnecessary arteriograms will be very few. At the present time arteriography in most institutions has less morbidity than biopsy. Therefore, arteriography is used for diagnosis. Biopsy for diagnosis in most institutions should be limited to those lesions which, clinically, are felt not to represent angiofibroma. In those

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hospitals where arteriography is not performed or the experience is limited, biopsy would be indicated for diagnosis.

ADJUNCTS TO SURGICAL REMOVAL

Adjunctive procedures are used to decrease blood loss at the time of surgical resection. Cryosurgery, estrogens, embolization, artery ligation and preoperative radiotherapy have been used as adjunctive measures.

Cryotherapy has not been effective in our experience. Only small lesions limited to the nasopharynx can be frozen sufficiently to reduce bleeding. These small tumors can be removed with minimal blood loss without cryotherapy.

Estrogen therapy has been advocated to decrease tumor size and vascularity prior to surgery. Schiff[1] and Walike and Mackay[2] demonstrated increased collagen tissue and reduced vascularity on comparing preoperative biopsy with postoperative specimens in patients treated with estrogens. Histological evaluation is not a reliable indication of decreased vascularity since sections from the same tumor specimen may show variable histologic vascular patterns. Christianson et al[3] noticed decreased tumor size, clinically, in five of seven cases treated with estrogens. In three of the five patients, pre and postestrogen arteriograms were reported as demonstrating decreased vascularity. Duckert et al[4] reported evidence of decreased tumor size as measured on CAT scan following estrogen therapy. Not all authors agree that estrogen will demonstrably reduce blood loss at the time of surgery. A recent patient with a recurrent angiofibroma with significant internal carotid artery blood supply received six weeks of diethylstilbestrol (15 mg/day). Comparison of pre and postestrogen CAT scans showed resolution of thickened inflammatory sinus and nasal mucosa and only slight decrease in the size of the tumor. Pre and postestrogen arteriograms demonstrated no change in the vascular pattern. In our experience, estrogens have had no clinical efficacy in reducing blood loss.

Embolization as an adjunct has consistently decreased vascularity of the tumors arteriographically and clinically. The size of the tumor does not change significantly. Embolization may be performed a few days prior to surgery or at the time of surgery. Gelfoam® or beads may be used. Experience is required to avoid reflux of emboli into the internal carotid artery when percutaneous catheterization is used. This risk, though small, has deterred the author from using the percutaneous technique. Embolization is reserved for large lesions which have both internal and external carotid blood supply or tumors which have intracranial extension that are deemed resectable. Embolization in these cases is performed at the time of surgery with direct external carotid exposure and proximal external carotid ligation, thereby avoiding internal carotid emboli. Transantral internal maxillary ligation is performed routinely for all other cases. Clinically, the amount of bleeding with embolization is less than with transantral ligation. The rationale for not performing embolization routinely as described above, is related to the necessity of external carotid artery ligation with resultant inability to perform subsequent arteriography for recurrent tumors.

Preoperative radiotherapy will diminish vascularity and frequently tumor size but is not used because of the potential sequelae in later years.

RADIATION THERAPY

Briant et al[5] advocate radiotherapy as the primary treatment of angiofibroma. This is an aggressive, radical approach for a benign lesion in young patients. Though sufficient time has not elapsed to determine the morbidity related to radiotherapy in the treatment of angiofibroma, there is sufficient evidence from observation of other benign conditions treated by radiotherapy that when alternative treatment is available, radiotherapy is contraindicated for benign tumors in young patients. The rationale for radiotherapy is based on the poor results with surgery. Briant et al state that the results of successful angiofibroma surgery at Princess Margaret

Hospital were 1 case in 19. It is unfortunate that the results of radiotherapy are compared to surgical results of earlier years when transoral avulsion or piecemeal removal of the tumor were the procedures usually employed. It is evident that in the past ten years with improved definition of tumor extent, determination of blood supply and appropriate surgical exposure, the results with surgery for extracranial disease are excellent. Christianson et al[3] report 79% cure with surgery, Boles and Dedo[6] 78%, Biller[7] 72%, Jafek et al[8] 90% cure with surgery. In the present series nine of ten patients were cured. With second procedures on those primary failures the percentage is increased to over 90%. It is our feeling that radiotherapy is contraindicated as a primary treatment modality for angiofibromas which do not demonstrate intracranial extension or extensive internal carotid blood supply. In most series intracranial extension represents approximately 5% to 10%. Radiotherapy is indicated in some patients who have intracranial extension. This is true if the intracranial tumor has significant blood flow from the internal carotid artery. Patients who have intracranial extension with minimal or no internal carotid artery supply, can be operated upon. The extracranial portion of the tumor is removed and the intracranial portion is followed postoperatively by CAT scans or arteriography. Postoperatively, if there is evidence of increasing intracranial size, then radiotherapy is indicated. Radiotherapy, therefore, is reserved for only a few select cases. In our experience it has been used in 1 of 12 cases, or 8%.

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HEMANGIOMAS OF THE HEAD AND NECK

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Hemangiomas are an interesting group of lesions which affect many anatomical structures of the human body. Interest today is confined to head and neck lesions which can occur in the infant, child or adult. Benign lesions affect the great majority of patients as contrasted to malignant ones. Diagnosis of the superficial lesions is usually made by inspection and palpation while additional diagnostic procedures (radiological studies and surgical exploration) may be indicated in patients with deep lesions.

Classification of vascular lesions of the head and neck should be designed to aid the physician in diagnosis and therapy. It should be understandable to all and in particular to those who are concerned with some phase of patient care. Satisfactory classifications also allow for coding and retrieval of patient data which can be used for clinical research.

Classification of hemangiomas of the head and neck may be oriented to histology, anatomy and pathogenesis for meaningful guidance and such groupings are presented below.

CLASSIFICATION

HISTOLOGIC

1. Hemangiomas
   a. Capillary
   b. Cavernous
   c. Mixed
   d. Invasive
2. Lymphangiomas
   a. Capillary
   b. Cavernous
   c. Mixed
   d. Invasive
3. Hemangiopericytoma
4. Intravascular angiomatosis (repair of thrombus)
5. Malignant angiosarcoma (Kaposi's sarcoma)
6. Vascular anomalies
   a. Congenital
      1) Venous aneurysms
      2) Congenital phlebectasia
      3) Arteriovenous fistulae
   b. Traumatic

ANATOMIC

1. Parotid
2. Oral cavity – tongue
3. Face – neck
4. Pharynx (naso-oro-hypo)
5. Larynx
6. Nose
7. Orbit
8. Osseous structures (skull, temporal and facial bones)

PATHOGENIC

1. Hematomas
2. Neoplasms
3. Anomalies
4. Vascular repair
   a. Traumatic
   b. Infection
   c. Thrombus and phleboliths

It is obvious that all vascular lesions listed cannot be discussed at this time, so this presentation will be limited to patients with the more common lesions.

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The discussion will include patients with visible and superficial lesions as well as those with deep lesions. Lesions of the pharynx, larynx and esophagus, although not visible, are considered superficial in relation to the regional mucous membranes.

Lastly, a satisfactory classification can aid the clinician in differential diagnosis so that a correct diagnosis can be made and the patient treated accordingly.

CASE PRESENTATIONS

Hemangiomas of the parotid gland are the most common tumor of this site in infants. Diagnosis is made by inspection and palpation. History may be relevant also, since soon after birth there is a period of rapid growth of the lesion. The whole parotid gland may be involved. In the head-hanging position the overlying skin often reveals bluish discoloration as well as a sensation of doughy engorgement to palpation. Treatment of choice is conservative observation.[1] Parents must be fully informed as to what to expect. It is rare indeed for the surgeon to be forced to perform surgery from the standpoint of infection, hemorrhage, ulceration or failure of the lesion to involute. Systemic cortisone and scarifying agents by injection are not recommended. The whole body surface must be examined for superficial skin hemangiomas.[2] If present these lesions may be the first to involute and hence can act as a prognostic clinical guide for the physician.[3-5] For those rare patients wherein the hemangioma does not involute, surgery may be indicated. The facial nerve is preserved. In those patients who have experienced surgery the microscopic examination of the removed tissue shows glandular tissue atrophy and venous channels (cases cited.)

Hemangiomas can occur on mucous membrane surfaces including the naso-, oro- and hypopharynx mucous membranes of the nasal chambers, larynx, esophagus and tracheobronchial structures.[6] The lesions are capillary, cavernous or mixed. Size may be a factor as to functional impairment. Subglottic hemangiomas in the infant may cause breathing difficulties necessitating tracheostomy. Decannulation can usually be done after involution of the lesion takes place.[7] Surgical excision may be indicated in certain other lesions associated with mucous membranes. In this instance, hemorrhage, infection or impairment of function are indications for surgery. Radiation therapy[8,9] can be and is used in some patients, remembering that in later years neoplasms may develop at the radiated site. This is particularly true when radiation is delivered at a younger age (cases cited).

Hemangiomas can occur in the soft tissues without surface marking. Thus patients have been encountered with deep lesions (deep in relation to the dermis and mucous membranes) of the face, neck and orbit. Likewise these lesions may be capillary, cavernous or mixed. Diagnosis can usually be made by inspection and palpation. Surgical excision is the treatment of choice in preference to radiation therapy (cases cited).

Hemangiomas of the tongue can be so large that there is functional impairment. In this instance there may be difficulties in eating, breathing and talking. The tongue may protrude and cannot be retracted. The mandible, maxilla and teeth may be deformed. Surgical excision of segments of the tongue may be the only treatment which will relieve symptoms through a reduction in size of the tongue. The surgical excision of portions of the tongue are planned to eliminate impairment of function. Tracheotomy is usually indicated during and after these surgical procedures (often more than one). Smaller hemangiomas of the tongue occur and, if symptomatic, can be excised in a wedge-shaped manner without functional impairment (cases cited).

A venous aneurysm of the parotid gland can occur[10] and one such patient was operated upon. Strome[11] reported this case in 1970. There is apparently an ectasia of venous channels in the vicinity of the parotid gland and within the gland itself. One large vein is responsible for the blood circulation to the ectatic portion. In the surgical removal once this "channel" is ligated the venous aneurysm collapses. The facial nerve is preserved (cases cited).

Venous aneurysmal bone cysts occur in bones of the face, mandible and skull. Etiology is perhaps related to trauma, infection or congenital causes. Swelling and tumor mass are characteristic. Radiograms are helpful in diagnosis showing rarefaction of bone. Surgery is the treatment of choice (case cited).

Lastly phleboectasia of venous channels can occur causing enlargement and engorgement of the parotid gland and surrounding tissues. There is no set pattern as to vessel arrangement. The head-hanging position may cause extreme engorgement and doughly swelling. This sign along with venograms is usually diagnostic. Venous channels are usually so diverse and large that surgery is not feasible, especially when the pterygomaxillary space and base of the skull are involved (case cited).

In conclusion, vascular lesions of the head and neck vary in size and anatomical location. Surgery may be the treatment of choice in some patients while observation may be indicated in others. Some vascular venous lesions are of such magnitude that surgery would endanger the patient's life. In these no curative therapy is available. In less forboding lesions some form of radiation therapy may be indicated. This modality must be used in carefully selected patients and in patients with capillary or small cavernous lesions. Cortisone has not been efficacious nor have sclerosing agents.

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CLINICAL CORRELATION OF ANOMALIES OF THE SUPRAGLOTTIC LARYNX WITH THE STAGED SEQUENCE OF NORMAL HUMAN LARYNGEAL DEVELOPMENT

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The clinical correlation of the authors' observations on human laryngeal development with existing literature supports the suggestion that earlier concepts, specifically by Frazer, may not be valid. It is further proposed that development of the human larynx may similarly correspond in man to that of the rat. Congenital laryngeal malformations are fundamentally associated with a disturbance of epithelial mesenchymal interactions, particularly related to a premature arrest of the normally vigorous epithelial activity.

1. The infant larynx has certain fundamental peculiarities of structure that must be considered in its examination and treatment.

2. Complete examination can be made only by the direct method. The difficulties of the examination are more apparent than real if the proper preparation, instruments and technique are used.

3. A method of measuring the larynx is offered. The most important measurement in the infant larynx is the subglottic diameter.

4. Tracheotomy conserves the laryngeal structure better than intubation in infants.

5. Symptoms of laryngeal disease in infants are frequently disregarded until serious secondary complications develop. Inspection of the larynx by the laryngologist will permit a correct diagnosis and save the lives of many infants.[1]

Although the infant larynx represents the first period of the clinical larynx, it is still only a later period of growth and development that began in embryonic life. It is the intent of this manuscript to establish a relationship with the Carnegie staging system[2,3] and the sequence of events of laryngeal development, but not to try and answer the question as to a *definite* mechanism of either normal or abnormal development. Correlation with the clinical and normal larynx will be estimated within the embryonic period although some reference will be made to the fetus.[4] It is not the function of this article to provide a detailed record of the early development of the larynx. Table 1 summarizes some of the key events that occur in reference to the Carnegie system of staging and classification of normal laryngeal development.

One of the ultimate goals of scientists throughout the history of medicine has been to establish norms related to the conditions of health and disease. To separate the normal from the abnormal was and still is the obsession of investigative minds in all spheres of intellectual life. Consequently, to compare an abnormal phenomenon with an established normalcy is an ideal circumstance. It is recognized that an individual norm does not provide an established reliable criterion for comparison, at least not in biological circumstances. An average norm based on the observations of a number of biologically similar individuals was introduced into medical science. This methodology with slight mod-

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TABLE 1. THE CARNEGIE SYSTEM STAGING OF NORMAL LARYNGEAL DEVELOPMENT

Carnegie Stage	*Approx. Age (days)*	*Length (mm) (Ca)*	*Pairs of Somites*	*Features*
1-8				Stages are based on the morphological appearance of the embryo or its covering (chorion).
9	20	1.5-2.5	1-3	Foregut is present, the median pharyngeal groove.[3]
10	22	2-3.5	4-12	Median pharyngeal groove includes the laryngotracheal sulcus and the pulmonary primordium at its caudal expansion.[3]
11	24	2.4-4.5	7.3-20	Pulmonary primordium divides into right and left lobes.[3]
12	26	3-5	21-29	Tracheoesophageal septum forms from endodermal proliferation of the lateral walls.[5] Mesoblastic elements of the larynx are massed caudal to the third pharyngeal arch where the superior laryngeal nerve terminates.[6]
13	28	4-6	30+	Endodermal central cells of the tracheoesophageal septum undergo necrosis.[5]
14	32	5-7		The epithelial lamina of the larynx forms. The hypopharyngeal eminence, the arytenoid swellings and first indication of the aryepiglottic folds appear. The site of the laryngeal inlet is identified.[3] The respiratory groove is transformed into a laryngotracheal conduit.[3,7]
15	33	7-9		Pharyngotracheal and vestibulotracheal canals are present.[3] The laryngeal inlet through active epithelial growth is y-shaped.[3] The superior laryngeal nerve has been identified.[8]
16	37	8-11		Hyoid condensation is beginning. The recurrent laryngeal nerve has been identified.[8] Cases of tracheoesophageal fistula have been recorded (stages 16-19).[5]
17	41	11-14		A definite larynx is seen.[5] The epiglottis is demarcated from the tongue (stages 17-19).[9,10*] Vestibular outgrowth appears.[9,10*] The cricoid begins condensation.[10,11*]
18	44	13-17		Hyoid condrifies.[10,11] Marked ventral cricoid condensations and thyroid lamina condensations appear.[9,11] Laryngeal musculature condensations are identified (i.e. posterior cricoarytenoid).[9]

*O'Rahilly R, Tucker J: The later development of the larynx in staged human embryos, unpublished data.

ifications, has survived the test of time and scrutiny. Although the extreme colors of the medical spectrum, the average normal and abnormal, are recognized in the professional mind, the gray area of the spectrum composed of anatomical and pathological variation is recognized with less intellectual certainty and less scientific comfort. It is customary to represent a medical value either as being within the boundaries of the standard deviation of its average norm, or less frequently, as being outside the boundaries of the spread of the normal deviation. We often recognize that some anatomical characteristics such as an excessive lateral folding of the epiglottis or a small cricoid ring fall into the category of anatomical variations. In some individuals, the same conditions are extreme and provoke a specific pathological state. This is justifiably considered an anomaly. It suffices to say that we have no reliable criteria other than clinical, to determine the level at which the anatomical variation meets those from the pathological range.

In the Carnegie system of classification, embryos are best arranged in 23 "stages," a technical term used to designate levels of development characterized by the appearance of specific morphological features, such as somites and eyes,[3] etc. In other words, one stage of development has something present that did not exist at the previous level of development (Table 1[3,5-11]).

Human prenatal, anatomical[12] and physiological development, as well as postnatal, anatomical, physiological, and emotional growth does not occur in a straight or smooth curve.[4] Rather, it is represented in individual organs, the entire organism by periods of intense activity with spurts of transformations followed by plateaus of lesser change and stability.

If one looks at the overall time of prenatal growth, that is the embryo and fetal periods together, it becomes apparent that morphologic development and physiologic function are oriented into discrete but somewhat overlapping periods.[4] During the embryonic period, growth is a highly sophisticated form of cellular interaction with resultant organ formation. The fetal period then represents not only an extension of maturation of embryonic organogenesis, but also is concerned with the establishment of physiologic activity and integration of organ systems.[4]

TABLE 2. CONGENITAL LARYNGEAL ANOMALIES

Type	*No. of cases*
Laryngomalacia	1415[13-19*]
Bifid epiglottis	8[20]
Absence of epiglottis	2[13]
Webs	224[13,14,16,21-31]
Atresia	43[32-34]
Cysts	52[14,35-37*]
Laryngocele	6[13,38]
Subglottic stenosis	278[13,14,39-50*]
Clefts	56[13,14,47-51*]
Hemangioma	95[52-54]
Total	2179

*Tucker J, Tucker GF Jr: Authors' statistics, 1978.

Like the respiratory system (larynx and pulmonary),[3] the extremities develop in proximodistal sequence,[3] first the limb buds, then hands, and then finger rays in the embryonic period. Continued fetal development yields functional bending of limbs, approximation of fingers, thumb-sucking movements and swallowing; the last being associated with physiologic laryngeal development. Swallowing-like motions have been observed radiologically in the human fetus of four months.*

OBSERVATIONS

A review of 2,179 recorded congenital laryngeal anomalies (Table 2[13-54]) illustrates the preponderance of laryngeal abnormality occupying the supraglottic larynx. Specific reference is made to congenital laryngomalacia and its variants. The multiple faces of this supraglottic deformity are evidenced by an epiglottis which may be mainly omega-shaped in character versus that which is markedly tubular. The latter may be short, or elongated on a broad base. The flaccid, flabby vibration of the lateral margins of the epiglottis (the aryepiglottic fold, and the supraarytenoid area) on inspiration creates stridor. The hazard of associating this symptom, stridor, with a specific disease is to ignore all other congenital laryngeal and paralaryngeal anomalies. This should be avoided by always performing a complete, direct (including the subglottis) laryngoscopic examination in the infant with stridor.

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*LaPayowker M: Personal communication, Temple University Hospital, Department of Radiology.

Of the total number of cases of congenital laryngomalacia (1,415), only four required tracheotomy.[13,14] Approximately two thirds of this group were male. The latter ratio is a consistent finding in other laryngeal anomalies and in tracheotomy in children. Of specific note is the Fearon and Ellis series[14] in which 5% of the cases that had laryngomalacia also had an associated subglottic stenosis. Only eight had bracheocephalic artery compressions, possibly reflecting a more diffuse cartilagenous development change to include the trachea.

Stridor is usually present from birth although as noted by Atkins[55] may not truly be observed until one or two months of age; the latter possibly being related to the dominance of nasal respiration in the newborn infant. The stridor may be intermittent or constant and is usually worse with the patient on his back. Pectus excavatum has been observed in an occasional case.[13] Fortunately, the stridor most often gradually subsides after 1½ years without specific therapy. Kelemen[18] in an extensive histologic review of congenital laryngeal stridor emphasized the edematous nature of the aryepiglottic folds, particularly the portion of the quadrangular ligament or membrane near the anterior attachment of the ventricular band. The suspensions of the epiglottis he states are extremely loose. Further, the plica-aryepiglottic fold can be completely void of musculature in a normal control as in a case with stridor. Three additional cases of congenital laryngeal stridor appear in the literature with associated premature calcification of the cartilages of the larynx and trachea.

The etiology of this condition is still unknown. Holinger and Brown[13] have suggested that the embryologic explanation for the extreme folding of epiglottis which originates from the base of the third and fourth arches may be the result of the more rapid growth rate of the third arch's contribution. This creates a long epiglottis which may tend to curl on itself. It should be noted, as recorded by O'Rahilly and Tucker[3] and observed by Walander,[56] that "much further work remains to be undertaken on early development of the pharynx, and a fortiori in other species."[3] Before the assignment of various laryngeal components to specific pharyngeal arches can be made, "it must be established that some of these arches actually exist."[56]

Kelemen[18] has pointed out that in man's evolution, the laryngeal vestibule has been left without an effective dilating muscle. However, histological examinations failed to demonstrate an anatomical abnormality.

Clerf, cited in Holinger and Johnston,[27] has suggested that the congenital laryngeal stridor is due to a developmental defect probably nutritional in origin.

Bifid Epiglottis. This extremely rare condition consists in cleavage persisting to at least two thirds the length of the epiglottis. This cleavage most often does not involve the tubercle. The epiglottic halves are well-supported, not obstructed to the airway. Laryngeal competence and aspiration may or may not be present with swallowing. Associated laryngeal anomalies with this condition have been subglottic stenosis, and multiple laryngeal cysts. It is particularly interesting to note that there is a 44% incidence of polydactyly in association with bifid epiglottis.[20]

Absence of the Epiglottis with Subglottic Stenosis. Two cases of absence of the epiglottis with severe glottic stenosis have been observed by Holinger and Brown[13] and Holinger et al.[57] This is indeed, a rare anomaly which represents the most infrequent anomaly within the entire cumulative series.

Laryngeal Webs. It should be noted that webs occur at all three levels within the supraglottic, glottic and subglottic endolarynx.[13,21] There is a statistically proven preponderance of glottic webs followed by the supraglottic and then subglottic.[14,21] The clinical picture at all levels is the hazard of airway obstruction. The supraglottic and subglottic web is a much less complicated problem as the dynamics of the glottis are not involved.

Laryngeal Atresia. Laryngeal atresia is an advanced form of laryngeal deformity. It certainly carries the most significantly hazardous prognosis.[5] Clinically the pharyngotracheal duct is most always intact with the exception of a case by Cohen.[32] This opening is clinically so small that it is not able to sustain life.

The symptoms of this condition needless to say are acute: dramatic, of short duration, and most often fatal. Jackson and Jackson,[58] Holinger and Brown,[13] and Cohen[32] have each reported a case that has survived the immediate presentation. Smith and Bain[33] reviewed 26 reported cases in the literature and added 9 of their own. These nine were all associated with other major congenital anomalies which probably in themselves were incompatible with life. They further classified laryngeal atresia into three types depending on the level of atresia: 1) supraglottic and infraglottic; 2) infraglottic; 3) glottic. The infraglottic and glottic atresias were mainly associated with a solid dome-shaped cartilaginous deformity of the cricoid cartilage. In most all types, a persistent, small pharyngotracheal duct is present.

DISCUSSION

All true developmental anomalies or teratogenetic effects are a result of disorder organogenesis.[59] It is only by mere chance that the embryologist has the opportunity to study an abnormally developed embryo.[59] The scientific explanation of anomalies, therefore, becomes a deductive process, correlated to the timing sequence of normal development.[59]

The most critical period in organogenesis[5,59,60] is during the stage of the organ primordia. Within this period the greatest potential for differentiation in growth exists; indeed, as noted by Smith, it is when the embryo is most sensitive to various noxious agents.[5] The primordium could thus be arrested. The degree of embryologic insult is, therefore, self-limited to the particular organ or organ system by the specific point of differentiation[5] at the stage when the injury occurs. The organ primordia represents a stage of "limit liability," duration and incidence. The greater number of stages of organogenesis, the greater the chance of anomalous or variant development, such as in the supraglottis with extension of normal epiglottic development into the fifth fetal month and the establishment of elastic cartilage.[4]

Table 3 illustrates the levels of congenital anomalies based on an anatomical, supraglottic, glottic and subglottic laryngeal distribution. Other methods of generally classifying laryngeal anomalies would be to specifically relate the anomaly to the tissue type; that is, cartilage, muscular, vascular, connective, or epithelial tissues, etc. As the majority of laryngeal anomalies involve more than one tissue type,[13] for the purpose of this presentation the accepted clinical nomenclature is probably best for interpretation and utilization of the current literature available.

The anatomical classification of laryngeal anomalies permits a regionalization of perspective in studying laryngeal growth. The supraglottic larynx accounts for the vast majority of laryngeal variation in anomalous growth. Organogenesis, in reference to the supraglottic larynx, is concerned mainly with two areas of development: 1) the epiglottis and 2) the laryngeal vestibule.[61]

The epiglottis is stated to arise from the hypopharyngeal eminence which forms at stage 13;[3] the latter representing a fusion of the anterior extremities of the fourth arches in the mesobranchial

TABLE 3. ANATOMICAL DISTRIBUTION OF CONGENITAL LARYNGEAL ANOMALIES*

Supraglottic		Congenital laryngomalacia	Congenital flaccid larynx Overdeveloped elongated epiglottis with broad base Excessive tubular short epiglottis Cri du chat
	Epiglottic	Bifid epiglottis Absence of epiglottis	
	Ventricular band Aryepiglottic fold	Webs Atresia "Congenital cyst" Hemangioma	
	Ventricle	Laryngocele	
Glottic	True vocal cords	Webs Atresia Vocal cord sulcus	
Subglottic	Infraglottic and cricoid	Stenosis Webs Atresia Cleft Hemangioma	

*Laryngeal cysts, paralysis and papilloma are excluded as they are not truly defects of laryngeal organogenesis.

field, the paired origin of the epiglottis.[7] However, others[3,56] have stated that the eminence should not be regarded as the epiglottic primordia until it is clearly demarcated from the tongue. This does not occur until stage 17.[9,10]* It would therefore appear that the most vulnerable time of potential organogenesis in the developmental organization of the epiglottis would be at stages 15 to 17. Disturbance at these stages would create a maximum effect in dysgenesis producing the clinical entities of absence of the epiglottis, bifid epiglottis, and possibly even the variants such as laryngomalacia. It should be recognized that the etiology of the laryngomalacia is more than highly speculative.

After the active formation of the epithelial lamina, development of the laryngeal vestibule begins with the establishment of the vestibulotracheal canal.[3]

Historically, embryologic development is based on the remodeling forces between mesenchyme and epithelium. A duality of conflicting opinion regarding the role of each still exists as recorded by O'Rahilly and Tucker.[3] Mesenchyme has been demonstrated to have a stimulating influence on epithelial morphogenesis.[62] Mesenchymal histogenesis in the mouse lung is dependent on epithelial association.[63] The epithelial mesenchymal interactions, though definite, are still poorly understood. Finally, the importance of demarcation between masses of mesenchyme and actively shifting epithelial borders is dynamic to normal development.[3,64] In recent years the importance of epithelial growth has been more appreciated and emphasized as compaired to the past dominance, in retrospect, of mesenchyme.

Frazer[65] pointed out in the 5 mm embryo, that the arytenoid swellings seem to extend forward, diverging to lie on each side of the epiglottis.[3] The latter mass (mesenchymal) effect creates a Y-shaped opening of the future laryngeal vestibule.[7]

By superimposing the outline of the

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*O'Rahilly R, Tucker J: Unpublished data.

median section of stage 14 and that of stage 15 it becomes apparent that the epithelial lamina had grown ventrally into previously unoccupied tissue and, hence, did not appear to be formed passively by the dorsal growth of the mesenchymal arytenoid swelling. Specifically, the lamina seemed to arise by active epithelial aggressive growth ventrally into the mesenchyme.[3]

Later, there is resulting cavitation and formation of the vestibulotracheal canal. Thus, cavitation represents a process of cellular necrosis which eventually forms the sculpturing of the normal differentiation[3] from stages 15-17.

"The vestibule is a consequence of epithelial proliferation,[3,56] which is strongest in the area between the fourth and sixth arches."[56]

The formation of laryngeal webs and atresia are related to a failure or variation of epithelial lamina growth,[61] necrosis of cells and/or lack of cavitation. This occurs approximately between stages 14 and 17. The mesenchyme appears to have a relatively passive role.[5]

CONCLUSIONS

"Although this hypothesis is partly speculative, there does seem to be sufficient evidence to doubt Frazer's concept of laryngeal development, and to suggest that the development of the larynx in man corresponds in its main essentials to that in the rat."[33]

"These congenital malformations are fundamentally due, it is suggested, to premature arrest of the normally vigorous epithelial activity."[61]

"Although the stage of onset of the disturbance can be determined within close limits, and its morphological stages can at least be subjected to reasonable conjecture, the causal factors that actually operate in individual human cases, by interfering with the growth process at the critical time, remain to be determined by clinical study."[5]

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OTOLARYNGIC PATHOLOGY TRAINING PROGRAM

A training program on otolaryngic pathology, presented by the Armed Forces Institute of Pathology (AFIP) in conjunction with the Committee on Otolaryngic Pathology, AAOO, is currently being offered at the Department of Otolaryngic Pathology, AFIP. The course covers both temporal bone pathology as well as surgical pathology of the head and neck area.

Requirements are flexible but preference is given to residents and practitioners in Otolaryngology and Pathology, both military and civilian, who wish to expand their knowledge of ENT pathology. The course, for which there is no charge, is designed to be given quarterly, beginning in January, April, July and October; however, consideration will be given to those seeking shorter training periods.

Requests for course applications should be directed to: The Director, Armed Forces Institute of Pathology, ATTN: AFIP-EDZ, Washington, DC 20306.

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SUBGLOTTIC STENOSIS OF THE LARYNX IN THE INFANT AND CHILD

METHODS OF MANAGEMENT

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This presentation is a ten-year retrospective study on all patients with proven subglottic stenosis admitted to the Department of Otolaryngology, Hospital for Sick Children, Toronto. Some of these patients have required no treatment, others one or two dilatations of the stenosis only; others tracheotomy only; some tracheotomy plus dilatations; some the Fearon-Cotton operation, and a few who had very extensive stenosis of the larynx and trachea, extensive reparative surgery. In this presentation, the authors describe the different types of management, and the results of treatment are assessed and compared.

A retrospective study has been carried out on all patients with subglottic stenosis of the larynx admitted to the Department of Otolaryngology, The Hospital for Sick Children in the ten-year period of 1966-1975 inclusive. Our objective was to attempt to determine the etiology, duration of symptoms before diagnosis, the most prominent symptoms and signs in these patients, methods of diagnosis, the type of management, and the type of surgical procedures carried out for the treatment of these patients.

Contentious points at issue are:

1. Just what is a true subglottic stenosis;
2. If and when the patient with stenosis should be bronchoscoped as well as laryngoscoped;
3. Whether active specific treatment should be instituted;
4. Whether a tracheotomy should be done;
5. Dilatations are to be the modality of treatment;
6. The frequency of and how long dilatations need to be carried out;
7. If and when open surgery should be done to correct the subglottic stenosis.

Other information would be the complications of dilatation, the complications of tracheotomy and complications of open neck surgery.

CASE STUDIES

In the ten-year period from 1966 to 1975 inclusive, from information obtained by the computer study, a total of 153 cases of subglottic stenosis was recorded as having been admitted to our department under the care of one of the eight members of the active staff.

In these patients the ages of gestation ranged from 34 to 44 weeks, 136 being 40 weeks or more in age, with a mean of 39.9 weeks. One hundred seven patients were male and 46 female. One hundred twenty-three (80.4%) were clearly congenital and seven were definitely acquired. In 23, partially because of inadequate information, the etiology of the stenosis was uncertain. Many of the children had multiple physical abnormalities. Forty-seven had other respiratory tract disease, 47 had cardiovascular anomalies, 23 had neuroskeletal deformities, 19 had neurological deficits and 5 had urogenital anomalies.

In 110 patients (71.9%) there was no history of laryngeal trauma. Forty-one (26.8%) of the 153 cases had been intubated. In one the etiology was external trauma. In only 20 of the 41 cases that were intubated was the length of intubation time recorded. Sixteen were intubated for less than six days with a mean of four and eight-tenths days. Only in 19 cases was the size of the en-

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dotracheal tube noted. The sizes of tubes ranged from 2.5 to 7 mm with a mean of 3.8 mm. As far as we could ascertain, polyvinyl chloride tubes were used for intubation in all cases. There were 18 deaths and 15 of these had tracheotomies. Six of the latter were thought to be related either to the stenosis or to the tracheotomy.

HISTORY AND DIAGNOSIS

Thirty-nine of the patients had been admitted to hospital before the diagnosis of subglottic stenosis was made, one or more times with the diagnosis of "croup." Seventy-four of the patients were reported as having intermittent stridor and four had continuous stridor before the diagnosis was established. Seventy-three of the patients either did not have stridor or at least there was no record made. In the 80 patients with stridor, 13 were cyanotic at the time of diagnosis.

Investigations on most of the patients prior to endoscopy included chest x-ray, soft tissue x-rays of the neck, esophagograms, blood gas studies and tracheograms. These studies were not particularly helpful in determing the degree of extent of the subglottic stenosis nor in deciding the type of treatment.

Management of Subglottic Stenosis. The diameter of the stenosis at the time of diagnosis has been by and large a visual estimation by the endoscopist. What is needed for this purpose is an accurate, sensitive instrument to measure exactly the lumen before and after instrumentation. Furthermore, there is lacking a method of gauging the vertical extent of the stenosis as well as the character of the stenosis. We have established that a thin, web-like stenosis, even when the lumen is of a small diameter, can be corrected by judicious dilatation, even on occasion with one dilatation. On the other hand, the greater the vertical extent of the stenosis, the greater will be the problem of treatment. If the stenosis extends beyond the confines of the cricoid cartilage, it is more likely that an external operation on the larynx will be necessary to relieve the airway obstruction.

In 134 cases, the reported sizes of the lumen of the stenoses range from the complete iatrogenic stenosis to one with a lumen of 5.5 mm. Six had a lumen of 2 mm, 34 of 2.5 mm, 43 of 3 mm, 31 of 3.5 mm and 18 of 4 mm. There was no correlation with age and so these figures are not too relevant in the comparison of the airways.

Seventy-two patients with subglottic stenosis required tracheotomy, 53 of these were urgent and 23 were elective. At the end of the ten-year period 58 (75%) were decannulated.

SURGICAL TREATMENT OF SUBGLOTTIC STENOSIS

In the preoperative management of subglottic stenosis, steroids and therapeutic doses were used in 85 of the patients and racemic epinephrine in 126.

Twelve patients were treated by dilatations without tracheotomy. Eleven of these patients needed one dilatation only whereas one other required four dilatations. Fifty-four of the tracheotomized patients were treated by dilatation. The frequency of dilatation varied from every two to six weeks. Forty-eight patients required 5 or less dilatations, 12 required 10 or less dilatations, 4 had 15 or less, whereas one patient had 60 dilatations and another 50 over a period of several years.

Serial dilatations were carried out in most cases with laryngotracheoscopes or bronchoscopes of graduated sizes.[1] The Jackson laryngeal dilators were used commonly as an adjunct to this treatment.

We were very conservative in the decannulation of tracheotomized patients under treatment for subglottic stenosis.[2] We have learned by experience, that although a patient may breathe quite well for a period of time through a relatively small subglottic lumen, the child may not be able to cope with the excess secretions of respiratory infections. Accordingly, before the tracheotomy is allowed to close, the tracheostome is kept patent by leaving a small plastic obturator or stent in the tracheotomy for a period of three months. The patient is sent home with this obturator in place along with a set of tracheotomy tubes. Should the patient develop respiratory difficulty, the obturator may be removed and replaced by the tracheotomy tube by the parent and without any delay.

If there has been no problem in this three-month period, the patient is readmitted for endoscopic examination and the tracheotomy is allowed to close.

One of us (W.S.C.) has reported a method of managing decannulation by the use of nasotracheal intubation for a period of time in certain problem cases.[3] This procedure is particularly suitable where there is an encroachment on the tracheal lumen by an inverted tracheal flap secondary to an upward pressure of the tracheotomy tube on the proximal trachea. The tracheotomy tube is removed and nasotracheal intubation is carried on for a period from two to five days before the nasotracheal tube is removed. Although prolonged endotracheal intubation in itself can cause subglottic stenosis, nevertheless the airway obstruction in certain problem cases of subglottic stenosis has been relieved successfully by this procedure.

The complications of laryngeal dilatations are relatively few. Two patients developed pneumothorax which was treated uneventfully by chest drainage and one patient had a pneumomediastinum which resolved spontaneously.

External Laryngeal Surgery for Correction of Subglottic Stenosis. When subglottic stenosis is not responding well to dilatation, then we believe an open procedure to attempt to correct the obstruction is justified. If the stenosis is very dense and especially if the upper tracheal rings and/or the glottis are involved, then dilatation alone is unlikely to accomplish a satisfactory result. Neither is such a stenosis likely to improve spontaneously. Furthermore, the cricoid cartilage itself may be abnormally small or abnormally thick, thus resulting in a small lumen. As yet we know of no satisfactory method of determining the character of the cricoid ring itself except by exposing it through an external surgical approach.

Fearon-Cotton Operation. The Fearon-Cotton operation was designed, after a research study on the primate larynx, to correct subglottic stenosis in those patients who do not respond to dilatation.[4-7] In this operation the cricoid and thyroid cartilages are exposed by an adequate collar skin incision at the level of the cricothyroid membrane. A vertical incision is made through the cricoid cartilage and the stenosis in or near the midline and thus entering the lumen of the cricoid. If necessary, one or more of the adjacent tracheal rings may be divided as well. Then, without internal stenting or surfacing, the ends of the cricoid are held apart, using the suitably sized piece of thyroid alar cartilage or a suitably shaped portion of autogenous rib cartilage.

Where the stenosis is very extensive and thus beyond the scope of the above described operation, we have used a variation of the Grahne technique.[8,9] This involves a median section of the thyroid and cricoid cartilages as well as the upper tracheal rings. The cicatricial tissue is resected and this is followed by a median section of the posterior cricoid lamina down to the esophageal musculature. Where necessary the interarytenoid muscles are divided as well. An Aboulker type of prosthesis extending from the vocal cords to the level of the tracheotomy is placed in the lumen of the larynx and the trachea beyond the tracheotomy opening. This prosthesis is retained by wiring a tracheotomy tube through a properly placed fenestra in the prosthesis. The laryngeal and tracheal incisions as well as the soft tissues are closed with catgut and silk sutures. The prosthesis is maintained in position for four months. At this point in time, of the six patients that required this operation, three have been decannulated uneventfully. In two of the three nondecannulated patients, at the time of operation, it was found that all the tracheal rings above the tracheotomy were completely destroyed, presumably because of chondritis. In spite of this an Aboulker prosthesis was placed in the larynx and trachea. In one, cadaver dura mater was placed over the stent with the hope that the dura would supply a lining for the trachea to replace the destroyed mucosa. We have found dura to be very effective for myringoplasties and perhaps it could be of value in the trachea. A third patient developed a stenosis at the upper margin of the prosthesis but this is responding well to dilatation.

SUMMARY AND CONCLUSIONS

A retrospective computer analysis has been carried out on the records of patients admitted to our department from 1966 to 1975 inclusive. It had been hoped that concrete information would be obtained regarding the etiology of the lesions, the factors responsible for stenosis following prolonged intubation, the most effective methods of management for specific types of stenosis, the length of time required to establish a safe airway, and the comparative results of treatment.

The information obtained from this analysis was too incomplete to provide all the answers that were expected. Unfortunately although computer figures are accurate, the information obtained is wholly dependent on the information supplied to the computer. The study did serve well to illustrate the inadequacies in the records of these patients and therefore the value of this study accordingly is limited. However, as a result, a protocol for an ongoing prospective study has been developed. We would like to see this type of protocol used in all other centers dealing with subglottic stenosis.

Our study has shown nevertheless that all patients with stenosis do not require active treatment; that some with reported severe stenosis improved without dilatation; that some patients could be dilated effectively without resorting to tracheotomy.

Many of these patients studied had other major physical abnormalities which complicated the management, and in fact several died of disease unrelated to the airway obstruction.

Although there is not general agreement among all the members of the staff in this department, we feel strongly that bronchoscopy should be carried out on all patients with stenosis in spite of the possibility of precipitating a tracheotomy. Our rationale for this is that some patients are helped by dilatation without tracheotomy and that if a tracheotomy is precipitated by the procedure, then that patient is in jeopardy from airway obstruction in the future, especially if respiratory infections should develop. Bronchoscopy itself provides a form of dilatation.

Finally, the authors have described methods of external laryngeal surgery for severe subglottic stenosis in patients who have failed to respond to conventional treatment.

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MANAGEMENT OF SUBGLOTTIC STENOSIS IN INFANCY AND CHILDHOOD

REVIEW OF A CONSECUTIVE SERIES OF CASES MANAGED BY SURGICAL RECONSTRUCTION

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The management of mature subglottic stenosis secondary to endotracheal intubation in infancy and childhood remains a controversial issue. If treated similarly to congenital subglottic stenosis by tracheotomy and a "wait-and-see" period then there is a considerably higher mortality and morbidity for the acquired disease compared with the congenital. Eighteen children with severe acquired subglottic stenosis managed by surgical reconstruction are presented; 17 have been successfully extubated. The longest follow-up is 5½ years. No evidence of interference with laryngeal growth is evident.

This study was undertaken to evaluate current management of severe subglottic stenosis in children secondary to endotracheal intubation at the University of Cincinnati Medical Center, with particular emphasis on surgical repair.

Until the past decade most cases of subglottic stenosis in infancy and childhood had been congenital in origin and had been satisfactorily managed by gentle periodic dilation with or without tracheotomy according to the severity of the lesion and needs of the airway. Holinger et al[1] reported in 1976 that tracheotomy was required in 44% of their cases of congenital subglottic stenosis. In 1965 McDonald and Stocks[2] advocated long-term intubation as an alternative to tracheotomy in the management of upper airway problems. Since then the number of cases of subglottic stenosis of the acquired type secondary to this practice has increased, and they form the largest proportion of cases of subglottic stenosis in infancy and childhood presently seen in clinical practice. This is a more severe form of stenosis than the congenital type and in the series reported by Holinger et al[1] in 1976 38 of 39 cases required tracheotomy. They conclude from their review in comparing acquired with congenital subglottic stenosis that the outlook for the acquired group is less favorable with a higher morbidity and mortality than the congenital group. Of the congenital group 44% required tracheotomy, 2.1% died due to tracheotomy complication and 10.8% had their tracheotomy in place at the time of writing. Of the acquired group 97% required tracheotomy, 11% died due to tracheotomy and 27.6% still wore their tracheotomy tube. The difference between these two diseases is certainly true in my experience and also that of others.[*] Here lies the crux of the problem: the accepted method of treating subglottic stenosis in the pediatric age group is by long-term tracheotomy with or without periodic gentle dilation: this management was based on experience with congenital subglottic stenosis, and is still correct management for this problem. With acquired stenosis, however, the disease is more severe. Mortality rates of between 11[1] and 24%[3] directly attributable to the tracheotomy have been reported in those cases man-

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[*] Fearon B: Personal communication.

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Presented at the meeting of the American Laryngological Association, Palm Beach, Florida, April 22-23, 1978.

TABLE 1. IATROGENIC SUBGLOTTIC STENOSIS REQUIRING TRACHEOTOMY (N = 27)

Reason for Intubation	*No. Patients*
Head injury	9
Croup	6
Neonatal care	5
Postcardiac surgery	4
Burn	3
Total	27

aged by this "wait-and-see" policy. The reason for this is presumably that the more severe the stenosis, the less the reserve airway above the tracheotomy, should this become occluded. For this reason some authors[4-10] have pressed for a more vigorous attitude towards treating these patients.

In 1971 I had the privilege of working with Dr. Fearon on the experimental correction of subglottic stenosis in infant primates and studying the clinical problem at the Hospital for Sick Children in Toronto. In 1974[7] we reported to the American Laryngological Association on some initial success with a trap door of thyroid cartilage interposed between the cut ends of the cricoid cartilage, with an update report in 1976.[11] Since 1972, the author has pursued the use of autogenous costal cartilage for certain selected children with severe anterior subglottic stenosis. For cases not suitable for this method of reconstruction, other methods have been used successfully.

METHODS AND MATERIALS

Twenty-seven cases of subglottic stenosis secondary to endotracheal intubation that have been personally managed by the author at Children's Hospital Medical Center, Cincinnati are reviewed. These cases include all those severe enough to need a tracheotomy for at least six weeks for the subglottic pathology secondary to endotracheal intubation; thus excluded from discussion are six cases of subglottic injury managed by dilation, endoscopic or laser resection of granulation tissue, together with steroids and antibiotics where appropriate, either with or without short-term tracheotomy (less than six weeks). These exclusions are made to emphasize the management of severe stenosis.

The initial disease process requiring intubation is analyzed in Table 1. Of the 27 cases, 18 required surgical correction of the stenosis, while 9 were not operated (Table 2). Of these nine, one died (six months posttracheotomy) six were extubated at times varying between 6 and 45 weeks and two still have their tracheotomy in place.

Of the 18 operated patients, 11 were reconstructed by the autogenous costal cartilage method to be discussed below, 3 by laryngotracheoplasty as described by Evans and Todd[9] and 4 patients using the Rethi[12] principle modified by Aboulker et al[13] and by Grahne.[4] In this latter operation, the Montgomery laryngeal stent was used in place of the Aboulker[13] prothesis (Table 2).

A comment on the frequency of the condition is required. Out of 18 patients in the operated group, 8 had their endotracheal intubations at Children's Hospital Medical Center (CHMC), compared to 5 out of the 9 patients in the nonoperated group. No figures are available to relate these 13 patients who developed subglottic stenosis at this center to the total number of long-term intubations in CHMC. As a general policy in this region long-term intubation is preferred to tracheotomy whenever possible in the pediatric patient. Of the 13 patients managed entirely at CHMC, all had tracheotomies performed because of inability to remove the endotracheal tube without immediate upper respiratory distress, unmanageable by medical methods.

The remaining 14 patients received their primary intubations at other institutions and were referred to CHMC for their further care. Eight arrived with a tracheotomy in place.

Operative Technique. The patient is anesthetized via the existing tracheotomy, and the neck extended by placing a bolster under

TABLE 2. CASES OF SUBGLOTTIC STENOSIS REQUIRING TRACHEOTOMY FOR MORE THAN 6 WEEKS (N = 27)

Reconstructed		*Nonoperated*	
Autogenous costal cartilage	11	Death	1
Laryngotracheoplasty	3	Extubated	6
Anterior-posterior cricoid split	4	Still with tracheotomy	2
Total	18	Total	9

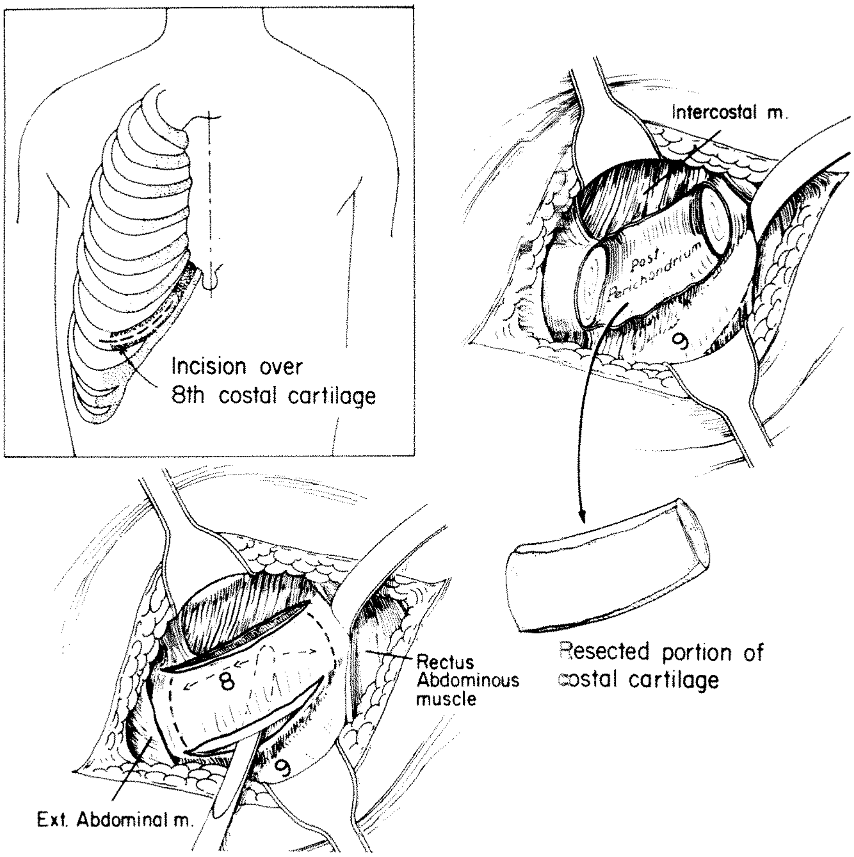

Fig. 1. Technique for obtaining costal cartilage graft. An incision is made through the perichondrium along the superior and inferior borders of a lower rib, taking care not to damage the cartilage. The remainder of the dissection is in the subperichondrial layer, leaving the perichondrium on the posterior aspect of the rib in situ.

the shoulders. The anterior neck and chest are prepped and draped. A suitable lower costal cartilage is selected and a 4 cm length of cartilage removed, leaving the lining perichondrium on one side of the cartilage (Fig. 1). The graft is placed in physiological saline solution, and the incision is closed. A dressing is applied and the area draped out of the surgical field for the rest of the case.

Two percent Xylocaine® with 1:100,000 epinephrine is injected into the soft tissues above the tracheotomy site, and the larynx is exposed by a horizontal skin incision centered on the cricoid. The cricoid cartilage is split vertically in the midline and the incision deepened through the intraluminal scar and lining mucosa to enter the subglottic lumen. Great care is taken to keep in the midline. This vertical incision is continued superiorly in the midline of the thyroid cartilage to a point immediately below the anterior commissure, which is not divided. The incision is continued inferiorly, strictly in the midline, through the upper two or four tracheal rings, depending on the length of the stenosis. This incision may or may not reach the tracheotomy site (Fig. 2). The intraluminal scar and lining mucosa is incised along the length of the stenotic segment keeping in the midline. No attempt is made to remove the scar, since to do so will produce a raw intraluminal surface. The concept of not removing the scar was strongly emphasized by Rethi.[12] A neurosurgical sponge is placed in the trachea above the tracheotomy to prevent leak of anesthetic gas and to stop secretions from the operative site from flooding the lower airway.

The costal cartilage graft is now shaped into an ellipse in such a way (Fig. 2) that: 1) the largest piece of cartilage that may conveniently be placed between the cut ends of the thyroid, cricoid and tracheal cartilages may be used; 2) the perichondrial lining is placed towards the lumen; and 3) the edges of the

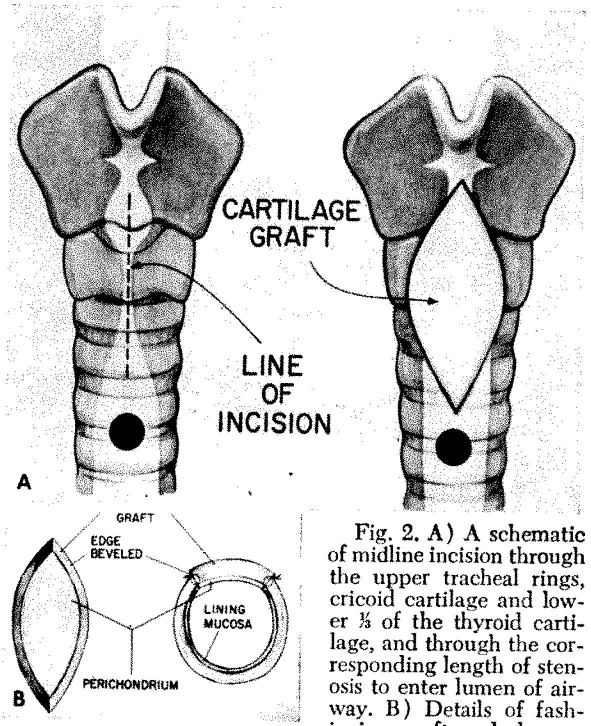

Fig. 2. A) A schematic of midline incision through the upper tracheal rings, cricoid cartilage and lower ⅓ of the thyroid cartilage, and through the corresponding length of stenosis to enter lumen of airway. B) Details of fashioning graft and demonstrating extramucosal placement of 5-0 prolene sutures.

graft are beveled to prevent "settling" of the graft into the lumen.

Prolene sutures (5-0) are used to sew in the graft using mattress sutures through cartilage placed extramucosally. Meticulous attention to detail during all phases of the operation is essential. The graft can be thoroughly immobilized by carefully placed sutures. The wound is closed in layers, leaving a small Penrose drain in place. Careful tracheal toilet is performed and bronchoscopy performed to assess the increase in subglottic and upper tracheal space.

RESULTS

All patients reconstructed at CHMC are reported as a consecutive series, divided into the three methods used. Of 11 consecutive patients on whom the costal cartilage graft operation was performed, ten children have been successfully extubated with a mean extubation time of 3.2 months (Table 3). If Patient 6 is excluded in this calculation the mean time for extubation is 2.2 months. The first two patients were able to plug a small sized tracheotomy tube approximately one month after surgery and wore a plugged tracheotomy tube without incident for four months, at which time they were extubated. With increasing confidence in the technique, there is a tendency towards earlier extubation. Patient 6 suffered from a head and neck injury and wore a tracheotomy tube plugged for one year postoperatively. Thus tracheal suctioning could be performed at times when his cough mechanism was inadequate. As neurologic recovery proceeded, however, his cough mechanism became adequate and extubation was accomplished.

Patient 10 is a relative failure. At the present time he wears a 00 Holinger tracheotomy tube plugged during the day and unplugged at night. He suffers from chondroepiphyseal dysplasia and is very small in stature. His cartilage is considerably calcified and microscopically abnormal.

There have been minimal complications. One patient developed a post-

TABLE 3. PATIENTS RECEIVING COSTAL CARTILAGE GRAFT FOR SUBGLOTTIC STENOSIS FOLLOWING ENDOTRACHEAL INTUBATION

A Consecutive Series

Patient No.	*Sex*	*Patient Age (yr)*	*Length of Intubation (days)*	*Watching Period from Tracheotomy to Reconstruction (mo)*	*Time for Extubation After Reconstruction (mo)*	*Follow-up (yr)*
1	F	1	10	12	5	5½
2	F	2	12	5	5	5
3	F	5	9	6	1½	5
4	M	2	10	6	2	4
5*	M	< 1	8	3	½	4
6	M	4	8	6	12	4
7	M	1	60	12	1	2
8	F	4	5	4	1	2
9	F	3	7	4	1	1½
10	M	10	4	3	X	½
11	M	7	12	4	3	½

*Eight-months.

operative pneumonia. There have been no cases of cartilage graft infection, nor any problems with settling of the graft into the lumen as described by Doig et al.[14] The voice of each patient is satisfactory and none is hoarse since the anterior commissure has not been violated.

The remaining seven patients, three operated by the Evans' technique[6] (Table 4) and four by the anterior and posterior cricoid split (Rethi principle)[12] (Table 5), are all satisfactorily extubated. Using the laryngotracheoplasty, the subglottic scar is excised and a Silastic® roll placed for six weeks. Evans and Todd[6] decannulated their patients approximately two weeks after endoscopic removal of the stent, and this has been my experience as well. All four of the anterior-posterior cricoid split patients had the Montgomery laryngeal stent in place for three months and required the removal of laryngeal granulomas between one and three times in the initial weeks following stent removal. Their voices, though satisfactory, are all inferior to those patients operated by either of the other two methods.

No patients have required reintubation. In fact, only one (Patient 8) out of the 17 extubated has required readmission to hospital for croup. There has been no mortality.

DISCUSSION

The need for these operations can be reduced by minimizing the number of children who acquire subglottic steno-

TABLE 4. PATIENTS OPERATED BY EVANS' TECHNIQUE FOR SUBGLOTTIC STENOSIS FOLLOWING ENDOTRACHEAL INTUBATION

A Consecutive Series

Patient No.	*Sex*	*Age (yr)*	*Length of Intubation (days)*	*Watching Period from Tracheotomy to Reconstruction (mo)*	*Time for Extubation After Reconstruction (mo)*	*Follow-up (yr)*
1	F	2	7	4	2	1
2	M	7	10	10	2½	½
3	M	1	23	6	2	½

TABLE 5. PATIENTS OPERATED USING ANTERIOR AND POSTERIOR CRICOID SPLIT (RETHI PRINCIPLE) FOR SUBGLOTTIC STENOSIS FOLLOWING ENDOTRACHEAL INTUBATION

A Consecutive Series

Patient No.	*Sex*	*Age (yr)*	*Length of Intubation (days)*	*Watching Period from Tracheotomy to Reconstruction (mo)*	*Time for Extubation After Reconstruction (mo)*	*Follow-up (yr)*
1	F	15	10	7	6	4
2	M	8	8	6	5	3
3	M	8	5	19	6	3
4	F	2	11	24	6	1

sis. With increasing use of endotracheal intubation in the management of airway problems, increased skill in the use of these tubes will occur so that damage to the laryngeal area is minimal. The skill of the intubator and a size tube which is small in relation to the larynx are certainly two of the most important factors affecting the incidence of subglottic stenosis secondary to intubation.

The reported success of laryngeal procedures in children[4,6-9] raises the issue of whether to operate or not, and if so, When should open operation be considered? The reported mortality of 11[1] to 24%[3] in patients with acquired subglottic stenosis is a cogent argument for the operation in these patients. The same argument does not apply to congenital subglottic stenosis. Thus Holinger et al[1] reported only one death out of 47 children needing tracheotomy for congenital stenosis, compared to four out of 38 in their children with acquired subglottic stenosis.

The arguments proposed against operative intervention are twofold. First, it is believed that as the laryngotracheal complex increases in size as the infant grows, there will be eventual outgrowth of the problem. While this may be true for congenital subglottic stenosis, neither clinical observation nor published data support this conclusion in stenosis secondary to endotracheal intubation. Thus Fearon and Cotton[3] reported that 26% of their patients (5 out of 19 survivors of long-term tracheotomy) still had their tracheotomy at the time of writing, which is remarkably close to the 28% (8 out of 29 survivors) reported by Holinger et al[1] in 1976. Evans and Todd[6] also commented on the delay in decannulating this group of patients. Any disease process that has a mortality rate in the range of 11-24%, and whose failure rate is in the range of 28% by conventional means, deserves to have alternative modes of therapy carefully evaluated.

The second argument is the traditional teaching that extensive surgery of the immature larynx interferes with normal growth.[15,16] Careful experimental data suggest this is not the case.* These studies support that of Calcaterra et al,[17] who report that midline vertical thyrotomy in dogs does not interfere with subsequent laryngeal development and vocal function. Initial work by Tucker et al** indicates that there are lateral growth centers in the cricoid cartilage. Further, none of the children operated have either functional, radiographic or endoscopic evidence that the larynx is failing to grow normally. Figure 3 shows a recent radiograph of Patient 1 in the series, 5½ years after her reconstructive surgery.

The question then, seems to be, When to operate? Certainly, every effort at early decannulation must be attempted prior to an open procedure. In the stage of active infection with subglottic granulation tissue, careful endoscopic bouginage, removal of gran-

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*Cotton R, Fearon B: Unpublished data.

**Tucker G, Tucker J, Ruben R: Personal Communication.

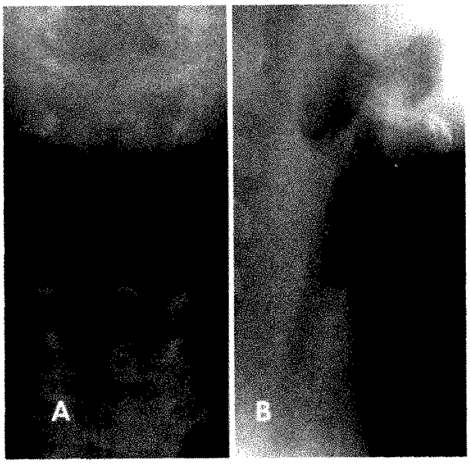

Fig. 3. A) Anterior-posterior and B) lateral radiographs of neck of Patient One, 5½ years after reconstruction. Notice normal subglottic space; narrowing is evident at site of tracheotomy which was in place for 17 months.

ulation tissue, steroids locally and systemically, culture and appropriate antibiotic therapy, together with time, may be sufficient to allow decannulation. If this is not possible within the first three months after injury, then bronchoscopy at that time will usually demonstrate a mature dense circumferential scar that does not admit a 2½ mm Storz bronchoscope. In most cases of this nature repeated dilation has failed to achieve extubation within a reasonable time period, in my experience. It seems illogical to expect to be able to dilate a circumferential scar surrounded by a ring of cartilage considerably thickened by perichondritis. If, however, the stenosis is thin, then dilation is often successful without the need for an open procedure. Endoscopic measurement is difficult, but in patients under the age of five, a subglottic lumen that cannot be dilated above No. 12 French gauge after three examinations should be considered for an open operation.

With regard to the choice of operation, careful preoperative radiologic and endoscopic evaluation is essential. Xeroradiography is used only in those cases when conventional radiography has not produced adequate information. All stenoses severe enough to consider an open procedure are circumferential. Most of them are eccentric with the greatest depth of pathology lying anteriorly, a few millimeters below the glottis and extending varying lengths down the trachea. All patients in this series had an identifiable lumen, albeit small: judicious dilation in the early stages of the inflammatory process aids in the establishment of a lumen. Provided there is not an accompanying glottic problem, such patients are selected for the autogenous costal cartilage graft. Length is not an issue since it has been demonstrated that long segments of cartilage may be successfully grafted to lengthy segments of tracheal stenosis in children.[18] It is likely that some of these patients with severe anterior stenosis not extending to the tracheotomy site could be operated successfully with a laryngotracheoplasty; in those patients who have little or no identifiable cartilage remaining anteriorly, or whose stenosis is long, the cartilage graft procedure is the method of choice. In those few patients where the bulk of the stenosis lies posteriorly and it is necessary to excise the scar, the laryngotracheoplasty with Silastic® stenting becomes the method of choice, again provided the glottis is normal. For combined severe glottic and subglottic stenosis the Rethi[12] operation should be considered, particularly when the posterior commissure and posterior subglottis are markedly affected.

It is pertinent to observe that resection of subglottic stenosis with thyrotracheal anastomosis is not to be recommended in children under 12 until more information is available about the growth of the anastomotic site. Preliminary work on tracheal resection and end-to-end anastomosis in puppies[19-21] and piglets[22] is not too encouraging.

Contraindications to surgery include any condition in which, even if the laryngeal stenosis were relieved, tracheotomy would still be necessary, for example, for tracheal toilet, or any combination of medical problems that would preclude successful rehabilitation at home.

CONCLUSIONS

Acquired subglottic stenosis in children secondary to intubation has a higher mortality and morbidity than congenital subglottic stenosis.[1] Reported mortality rates related only to deaths attributable to the tracheotomy range from 11-24%, while failure to decannulate occurs in 26-28% of cases treated conservatively. Alternative methods of therapy therefore should be carefully evaluated.

The rationale for recommending surgical reconstruction in cases of severe acquired subglottic stenosis is the reported mortality associated with the "wait-and-see" policy. Not all cases of mature subglottic stenosis require open reconstruction. This should be reserved only for severe cases. Mature stenoses that are thin often respond to gentle dilation.

Severe laryngeal stenosis in children is amenable to surgical reconstruction, though no single operation is suitable for all cases. Eleven consecutive patients with severe anterior subglottic stenosis managed by autogenous costal cartilage graft interposition to cricoid and upper trachea are presented. Ten have been extubated.

Three consecutive patients with posterior subglottic stenosis managed by the Evans' technique and four consecutive patients with posterior glottic and subglottic stenosis managed by the Rethi principle using a Montgomery laryngeal stent have all been extubated. There has been no mortality.

Though continued growth of the laryngotracheal area is difficult to document in the living patient, animal data suggests that operating on the thyroid and cricoid cartilages of infant primates or puppies[17] does not interfere with the growth potential. In the clinical material, the longest follow-up is presently 5½ years: in none of the cases reported is there any clinical, radiographic, or endoscopic evidence of reduced laryngeal growth potential secondary to laryngeal surgery.

Those cases of severe laryngeal stenosis secondary to intubation that have failed to respond to conservative management should be considered for a laryngotracheal reconstruction appropriate for the pathologic problem. Each case should receive careful individual evaluation. The morbidity and mortality of cases managed in this way is considerably less than if managed by the "wait-and-see" policy.

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SECOND INTERNATIONAL SYMPOSIUM ON OTITIS MEDIA WITH EFFUSION

CALL FOR PAPERS

The Second International Symposium on Otitis Media with Effusion will be held May 9-11, 1979 at Ohio State University, Columbus, Ohio. Papers on the following topics will be considered by the program committee:

I. Definition and Classification

II. Epidemiology and Natural History

III. Etiology and Pathogenesis (Tubal Physiology and Pathology; Surface-Active Agent; Anatomy, Morphology, Pathology; Biochemistry, Pharmacology; Microbiology and Immunology)

IV. Identification, Diagnosis and Screening (Tubal Dysfunction; Microbiology for Bacterial Infection, Sensitivity Tests, Allergy; Biopsy and Cytology).

V. Management (Medical [Antibiotics, antihistamines, steroids, etc.]; Surgical [T&A, A, Tuboplasty, Ventilating Tube]; Educational management).

VI. Prevention (Vaccine, etc.)

VII. Outcome (Sequelae).

Please send a one-page abstract by September 1, 1978 to: David J. Lim, MD, Department of Otolaryngology, Ohio State University Hospitals, 456 Clinic Drive, Columbus, OH 43210.

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MANAGEMENT OF CHOANAL ATRESIA WITH THE CARBON DIOXIDE LASER

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Congenital choanal atresia frequently demands immediate recognition in the newborn, and provision of a nasal airway as soon as possible. A variety of techniques are available to correct this problem, but none is entirely satisfactory. Transpalatal procedures are associated with significant morbidity in the newborn, and transnasal microsurgical procedures are less predictable when a thick bony plate is present in the choanal obstruction. Transnasal resection with the CO_2 laser has been carried out in seven patients (ten sides), whose ages ranged from 16 hours to 14 years. From this early experience, it appears that the procedure is entirely feasible and convenient. It seems to have significant advantages over conventional microsurgical techniques. Eight out of ten choanae have remained patent for four months or more. A lumen keeper is needed during the immediate postoperative period for at least two to three weeks. The procedure is associated with minimal morbidity.

Choanal atresia was first recognized by Roederer in 1775.[1] It is a congenital lesion that occurs in approximately one in 8,000 births. The first reported surgical procedure to correct this deformity was performed by Emmert in 1851, and was described as the passage of a trocar and cannula through the obstruction.[2]

The atresia may be either bony or membranous, with approximately 90% of the cases being the former. It is traditionally thought that this defect is more common in females, and more often occurs unilaterally.[3] Many of these patients have multiple congenital anomalies as well.[3]

Etiology. Although the exact etiology of choanal atresia is unknown, it is presumed that partial or complete persistence of the buccopharyngeal membrane is responsible; it seems to explain the membranous type best. A medial and vertical overgrowth of the palatine bones may be the cause in cases of bony atresia. Some feel, however, that the atresia is a teratogenically induced anomaly because of the associated craniofacial anomalies seen in some patients.[4]

Diagnosis. The diagnosis of bilateral choanal atresia is usually made in the first few hours of life. Being obligate nose breathers, these children characteristically develop severe respiratory distress, which is relieved either by crying or by the establishment of an oral airway.

The diagnosis is confirmed by various maneuvers. If choanal atresia is suspected, attempts should be made to pass a No. 6 French catheter through the nasal passage into the pharynx, after appropriate topical vasoconstriction. Methylene blue dye may also be instilled in the nose while observing the pharynx for the appearance of dye. The use of a hand-held otoscope, with an ordinary ear speculum, may give excellent visualization of the atresic area. This also enables the examiner to palpate the atresia to determine whether it is bony or membranous. Another reliable method of diagnosis, however, is the use of contrast radiography after

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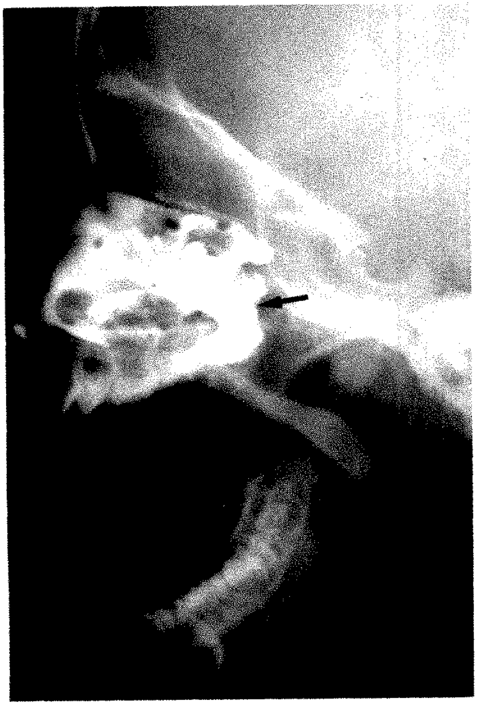

Fig. 1. Lateral radiograph demonstrating inability of dye to pass into the pharynx. Arrow indicates point of atresia plate.

applying a vasoconstrictor agent to the mucous membrane (Fig. 1).

In cases where the neonate has survived the first 24 hours of life undiagnosed, feeding difficulties become conspicuous; these children have severe difficulty in sucking.

Unilateral choanal atresia may not be diagnosed until later in life. It frequently presents with persistent unilateral nasal obstruction with mucoid discharge. Commonly, this condition is misdiagnosed as a foreign body or sinusitis.

Treatment. Bilateral atresia requires immediate establishment of an oral airway, either with a McGovern nipple or an oropharyngeal airway. Gavage feeding must also be undertaken to maintain proper nourishment. Neither prolonged intubation nor tracheotomy is warranted.

A variety of surgical procedures have been used in the treatment of this disease. The first reported procedure was transnasal.[2] Since then, many approaches have been advocated.[5-8] Recently, the use of the operating microscope in conjunction with the transnasal approach has been used.[4] This appears to be the most promising method of approaching this difficult lesion, especially in the neonate.

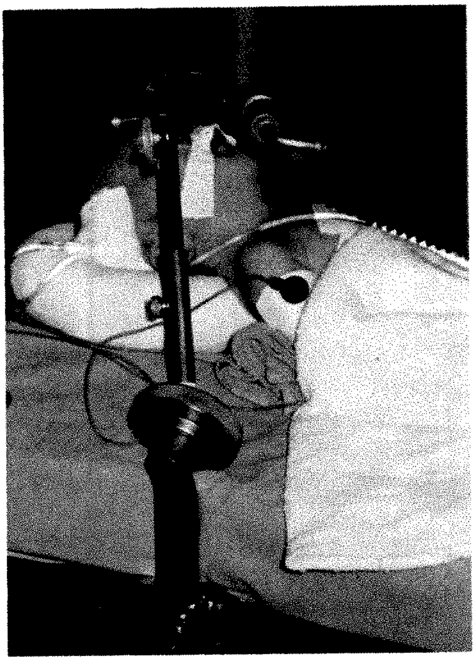

Fig. 2. Neonate in hyperextended position with nasal speculum in place being held by otologic speculum holder.

The timing of treatment also has been a subject of debate. Some feel that immediate treatment should be undertaken via the transnasal route by simply puncturing the atresic plate. Definitive treatment is undertaken via the transpalatal route at a later date. Others have advocated the immediate correction through the transpalatal approach even in the newborn.[6]

Since the carbon dioxide surgical laser was coupled to the Zeiss operating microscope in 1969, it has been used to treat multiple and varied lesions of the upper respiratory tract.[9] Because of its unique features, it is now apparent that this system is a most effective means of treating lesions of the pediatric airway.[10]

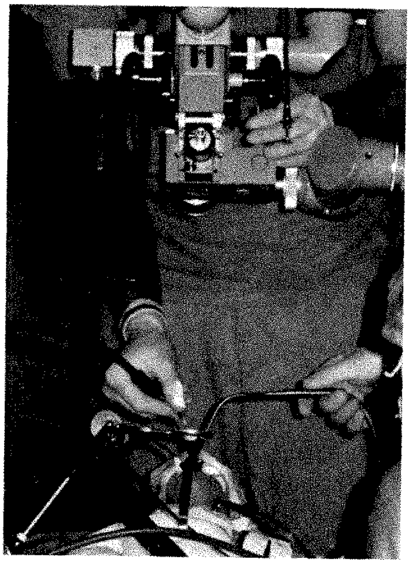

Fig. 3. Microscope and laser in position directly over nasal speculum. Surgeon controls beam while viewing lesion directly.

The transnasal application of the carbon dioxide surgical laser is now proposed as an alternative method of resecting the atresic area. We have employed this modality in the treatment of choanal atresia since 1976.

METHODS AND MATERIALS

Seven patients, six females and one male, with the diagnosis of choanal atresia underwent operation with a 50 watt carbon dioxide laser.* All patients were operated upon under general anesthesia, using a small bore orotracheal tube, protected with aluminum tape.

Topical vasoconstriction of the nasal tissues was accomplished with a 0.125% or 0.25% solution of phenylephrine hydrochloride after clearing the nose of secretions.

The patients were then placed in the supine position, with the shoulders elevated and the head hyperextended. A modified ear speculum with a fiberoptic light source was placed in the nasal cavity, and retained in position with a standard otologic speculum holder (Fig. 2). The operating microscope with the attached laser was then directed along the floor of the nose (Fig. 3), and the atresia visualized (Fig. 4A). A saline-soaked neurosurgical sponge was placed in the nasopharynx to protect the eustachian tubes and mucous membrane once the artesia was opened.

The atresia area was gradually vaporized with the laser until the neurosurgical sponge could be visualized in the nasopharynx (Fig. 4B). The sponge was then used as a landmark, and the choana was gradually enlarged to the desired size, depending on the age of the patient. The dissection was completed in a few minutes if the atresia was merely membranous. Frequently, a partial bony plate was encountered which was removed in part by the laser and in part with a small rongeur in order to avoid overheating of the adjacent tissues; dissection of the bony plate required a few extra minutes. Dissection was terminated when the septum was exposed medially, the floor of the nose inferiorly, the sphenoid superiorly, and the pterygoid plate laterally. Stents of polyvinyl tubing or Silastic® sheeting were then placed and sutured to the membranous septum with a mattress suture of nylon. Stenting was maintained from two to six weeks. If polyvinyl tubing was employed, the outer ends were beveled in an upward direction for ease of suctioning and proper cleaning. Adequate humidification was provided in an attempt to reduce crusting of the stent material.

RESULTS

Six females and one male patient underwent laser excision of their choanal atresias. Of these, three were bilateral and four were unilateral, making a total

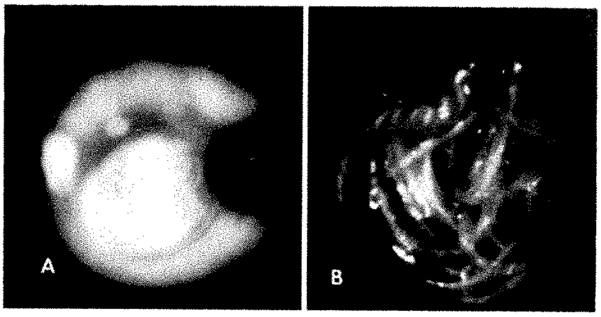

Fig. 4. A) Microscope view of bony atresia plate. B) Neurosurgical sponge in the nasopharynx, appearing through newly created opening in atresia plate.

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*American Optical, Buffalo, New York.

TABLE 1. RESULTS IN SEVEN PATIENTS

Age	*Sex*	*Side*	*Type*	*Period of Stenting*	*Results*	*Follow-up Period*
16 hr	M	Bil.	B	6 wk	1. One side open 2. One side closed req. 2nd op. at 2 mo	1. Open @ 15 mo 2. Open @ 12 mo
24 hr	F	Bil.	B	6 wk	1. One side open 2. One side closed req. 2nd op. at 2 mo	1. Open @ 13 mo 2. Remains closed
8 mo	F	Bil.	M	2 wk	Both sides open	Open @ 4 mo
3 yr*	F	R	B	4 wk	Open	Open @ 12 mo
9 yr	F	L	M	None	Open	Open @ 24 mo
10 yr*	F	L	B	3 wk	Open	Open @ 14 mo
14 yr	F	L	B	4 wk	Closed	Remains closed

Bil. - Bilateral; R - Right; L - Left; B - Bony type; M - Membranous type.
*Prior transpalatal procedure.

of ten obstructed choanae. Follow-up ranged from 4 to 24 months. Seven choanae have remained completely open, without requiring further therapy. Three choanae closed postoperatively. A second laser procedure was performed on two, one of which remains open at 12 months. The third patient, a 14-year-old female, closed immediately after removal of her stent; no further attempt to reopen this has been made (Table 1).

DISCUSSION

Various approaches to the correction of this troublesome problem have been advocated in the past. Those utilizing the transpalatal approach are formidable operations. Most of the transnasal approaches have been "blind," and therefore, risky. Previously described microsurgical procedures have been time consuming, mostly due to bleeding which tends to obscure the operative field.

The use of the carbon dioxide surgical laser in this procedure has several distinct advantages. The equipment necessary to gain access to the nasal cavity is quite simple and easily assembled. The *rapidity* and *accuracy* with which the operation can be performed is quite unique. This is in large part due to the hemostatic effect of the laser, and therefore, to the lack of "nuisance" bleeding.[11]

Postoperative edema from laser surgery is conspicuous by its absence.[11] This is important in neonatal tissues where the dimensions of the choana are small.

Laser wounds heal on schedule with minimal postoperative scarring. Experimentation has shown that small lesions will reepithelialize at between 10 and 12 days. This enables removal of the stent in two to three weeks.[11]

Failures apparently have been due to the occurrence of granulation tissue in the operative site, after stenting over a traditional six-week period. More recently, we have employed stents over a shorter time span of between two and three weeks. Leaving stenting material longer than this may contribute to an inflammatory response, the development of granulation tissue, and restenosis.

In the 14-year-old patient, whose newly created opening closed, it was found that only a 6 x 4 mm opening could be created through the thickened bony plate; this was in part due to the deviation of the posterior edge of the bony septum toward the obstructed side. Under these circumstances, a transnasal operation is not likely to be successful; a transpalatal operation, on the other hand, allows resection of the posterior edge of the septum, and is more assured of success.

If thin bone is encountered in the atresia, it can be excised with the laser; however, if the bony plate is 1 mm or more in thickness it should be excised with a microrongeur similar to that used in transnasal hypophysectomy. The use of the rongeur rather than the laser avoids the problem of overheating of the adjacent bone by the laser beam, with resulting sequestration, granulation tissue formation, and secondary stenosis.

It appears that the carbon dioxide laser provides a convenient, atraumatic, and effective means of correcting congenital choanal atresia. There have been no complications due to the use of the CO_2 laser. Larger numbers of patients will be required before definite conclusions can be drawn as to whether long-term results are superior to previously described methods.

CONCLUSIONS

1. Choanal atresia continues to be a difficult congenital problem causing respiratory distress in the newborn.

2. All previously described techniques have some undesirable features and limitations.

3. The unique properties of the carbon dioxide laser make it most suitable for surgery of the neonatal airway.

4. The laser has been used successfully in correcting choanal atresia in an orderly and precise manner.

5. It appears that stenting may be needed for only two to three weeks postoperatively.

6. Further application of laser surgery in this condition will be required before final conclusions can be reached.

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CYCLIC PHARYNGEAL LYMPHOIDITIS: IMMUNOLOGICAL CONSIDERATIONS

JOSEPH L. GOLDMAN, MD
NEW YORK, NEW YORK

This communication presents the concept that recurrent infections of the lingual tonsils, lateral pharyngeal lymphoid bands and lymphoid follicles on the posterior pharyngeal wall, occurring with the same periodicity, is a cyclic clinical and immunological entity. These patients lacked resistance to the normal flora of the nasopharynx and pharynx. They were accordingly treated with a mixed respiratory bacterial vaccine, administered intradermally and according to a formulated program, to improve resistance or immunity of the lymphoid tissue. These patients showed definite improvement by this method of therapy. It is suggested that the effectiveness of therapy was accomplished through the immunological process of cell-mediated immunity. The immunobiologic development of cell-mediated immunity by T thymic-dependent cells and humoral immunity by B cells is briefly discussed.

What appear to be significant observations have been made on lymphoid tissue of the pharynx over the past 46 years. Our colleagues of a century ago were concerned with techniques of removing and reducing the lymphoid tissue of the pharynx and methods of controlling bleeding. This new concept is a point of view which may be fitting for 1978.

I wish to state at the outset that this presentation will be unscientific, provocative and even open to questions. It is not a double-blind study nor does it involve a proven method of therapy. It is, in a sense, a personal, medical communication. It does represent, however, a particular type of pragmatic observation which has made a deep impression on me. The subject is involved with the nature of recurrent pharyngeal lymphoidal infections, the treatment I have used and the immunological implications.

The immunological considerations, whether correct or not, are very much in order at the present time. The continually increasing facets of immunobiology are making their inroads into every discipline of medicine, and we should realize that otolaryngology is included in this assault. I use the word assault to express strongly the opinion that the whole concept of disease and modalities of therapy will change radically when immunobiology will be transferred from theoretical and investigative areas to the practical areas of medicine. When this happens medicine will experience, I believe, its greatest advance.[1-7]

After my residency, I was exposed to a year's fellowship in bacteriology and immunology with Dr. Gregory Shwartzman. This exposure had a profound effect on my thinking about disease processes. It undoubtedly influenced my perception of pharyngeal lymphoidal infections. I trust that you will accept these observations just as experiences which, for me, have resulted in a new interpretation and approach to a problem.

In the first place, I have separated, or classified, pharyngeal lymphoiditis under consideration into three groups: lingual tonsillitis; infection and hypertrophy of the lateral pharyngeal bands of lymphoid tissues; and hypertrophy or swelling of lymphoid follicles on the posterior pharyngeal wall with varying degrees of discoloration. Acute tonsillitis in infants might be included.

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Presented at the meeting of the American Laryngological Association, Palm Beach, Florida, April 22-23, 1978.

What impressed me particularly in my early observations, on analyzing these pharyngeal infections, was their cyclic character. There was the persistent tendency to recur every four, six or eight weeks, regardless of the effectiveness of the primary treatment. The time of recurrence in individual patients had the same periodicity. I am certain that many, on reflection, have made the same observation, but to my knowledge there is no record of this clinical concept in the literature, otolaryngologic or immunobiologic, and I believe that it is an immunobiologic phenomenon.

Twenty-nine cases of pharyngeal lymphoiditis have been picked at random from my charts. I am using these cases essentially for illustrative purposes. Twelve were cases of acute lingual tonsillitis, 12 cases of acute infection of the lymphoid tissue of the lateral gutters of the pharynx and 5 cases of infected, hypertrophied, lymphoid follicles of the posterior wall of the pharynx. I have seen considerably more of these cases but I could not isolate them from my files.

The infections of the lingual tissues were frequently associated with white purulent spots and fever as high as 39.4 C. The patients with the infected lateral bands and hypertrophied follicles complained primarily of sore throat and lassitude, and low grade fever was often associated.

It was soon observed that specific infecting microorganisms were unimportant insofar as recurrences were concerned. Rarely was the same microorganism found in subsequent infections in the same patient. However, one or another of the pathogenic microorganisms of the upper respiratory flora was invariably isolated. The question of viral infections, a very broad subject, will not be discussed in this paper.

The issue which presented itself had to be evaluated in the following terms: Was there anything different or unusual about these pharyngeal infections? It seemed to me that I was dealing with a lack of normal resistance, or immunity, of the pharyngeal lymphoid tissue to the usual pathogenic bacterial flora of the pharynx or of the nasopharynx, to be more specific. Resistance would diminish progressively after each bout of infection with presumably acquired immunity.

Part of my early work in studying the flora of the nose and nasopharynx in health and in disease showed that, in healthy individuals, the nose did not contain pathogenic microorganisms while the nasopharynx did in the same persons.[8,9] I regarded the nasopharynx as the carrier-focus of pathogenic microorganisms, and the prominent pathogenic microorganisms would vary with seasons. Infections of the nose and sinuses and trachea and lungs would occur, as I see it, when the protective mechanisms of these organs broke down and invasion of microorganisms from the nasopharynx would occur. It may be of interest to relate that the pneumococcus was predominant from January through March, the months that pneumonias occurred, and the *Streptococcus hemolyticus* from March to June, the months that acute mastoiditis used to be operated on. This remark deserves mention only to illustrate the feature of specificity of microorganisms which is such an interesting phenomenon in bacterial infections and many immunological reactions. Of further interest to us, for instance, is the fact that over 90% of lateral sinus thrombosis is caused by the *S. hemolyticus*, and that of the pneumococci, only Type III can be the etiologic agent responsible for lateral sinus thrombosis.[10]

Thus, to return to our premise and subject that pharyngeal lymphoiditis could have been cyclic and this was due to lack of normal resistance of this tissue to the normal bacterial flora of the pharynx and nasopharynx, the next logical thought was to consider means to improve the resistance of the pharyngeal lymphoid tissue so that the cyclic nature of these infections would be altered or stopped. Having been impressed and influenced by the writings of Metchnikoff,[3] the famous Russian biologist, on phagocytosis and cell-mediated immunity and the value of vaccines by intradermal injections, I decided to treat these patients with mixed bacterial vaccine by intradermal injections. It is of interest that as early as 1908 Metchnikoff and Ehrlich jointly were awarded the Nobel Prize for Medcine and Physiology, the former for his work on cell-mediated immunity and the latter for his work on humoral immunity, even though now immunology is still in its very early stage of development as a scientific discipline.

Also, my attitudes about using vaccine were strengthened by my experience with a five-year project from 1932 to 1937 by using both stock and autogenous pneumococcus Type III vaccine on the same patient in conjunction with surgery to prevent meningitis in 56 cases of acute pneumococcus Type III mastoiditis.[11] Six intradermal injections at the rate of two a week were administered in the following increasing doses: 0.1, 0.2, 0.3, 0.5, 0.8 and 1 cc. If delayed local reactions (48 hours) were larger than the size of a 25-cent piece, the dose was not increased. The concentration was 600 million microorganisms per cubic centimeter. The mortality of meningitis associated with pneumococcus Type III mastoiditis at The Mount Sinai Hospital was reduced from 22% during the previous five years to 4%. Agglutinin, precipitin, complement fixation and other tests failed to show humoral antibodies in our patients and we concluded that active cellular immunity was responsible for reducing the mortality.

To indicate the potential effectiveness of pneumococcal vaccine, the experimental work of Barach[12] in 1928 might be mentioned. He showed that mice could be actively immunized in three days by a single intraperitoneal injection of Type I and II pneumococcus vaccine. In 1931 Barach[13] demonstrated the appearance of specific protective substances in human sera four or five days after intravenous and intradermal injections of pneumococcus vaccine. In cases of lobar pneumonia it was possible to evoke type-specific antibodies by the injection of heterologous types of pneumococcus vaccine. This is of interest at present because it has been recently reported that the incidence of pneumococcal pneumonias can be reduced by pneumococcal polysaccharide vaccines.[14]

In 1927, Tillett[15] was successful in actively immunizing rabbits with Type III pneumococcus vaccine. Especially significant in Tillett's experiments was the fact that he was able to obtain immunity in animals to Type III pneumococcus infections in the absence of specific antibodies in the blood serum.

The recent investigation of the use of vaccines conducted by the Food and Drug Administration deserves special comment.[16] I cannot resist making the statement that the report of the panel conducting the investigation is, in my opinion, far more unscientific than the scientific criticism the panel presents about vaccines. This concerns the practice of medicine very seriously and members of the medical profession should become aware of the report and do what they can to alter the final rules which will be issued in a few years. The FDA wishes practicing physicians to furnish them with information to indicate the true and specific value of vaccines. I trust that this report will be a contribution in this direction.

The following is the method of therapy I employed. The vaccine, used since 1932, was Combined Vaccine No. 4 with Catarrhalis (V-151),[*] which contains *Neisseria catarrhalis, Klebsiella pneumoniae, Diplococcus pneumoniae,* streptococci, and staphylococci. This vaccine has been removed from the market. According to Lilly & Co., they have stopped making this biological product; according to the FDA panel, the license to make this vaccine was revoked because there was no substantial "evidence of safety or effectiveness." This has not been my experience, and in reading the panel's report, I do not believe that their information has been adequate or correct. I am now using Bacterial Vaccine Mixed Respiratory.[**]

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[*] Eli Lilly and Company, Indianapolis, Indiana.

[**] Hollister-Stier, Division of Cutter Laboratories, Inc., Spokane, Washington.

The microorganisms of this vaccine are similar with those in Lilly's vaccine except there are twice as many staphylococci. The panel recommended that the license to make this vaccine be continued "on an interim basis in accordance with the appropriate Federal regulations and recommendations of this report."

I have found it necessary to dilute both the Lilly and Hollister-Stier vaccines ten times in order to avoid undesirably strong reactions in some patients from the very outset. The ideal arrangement is to inject the patients twice a week and the period can be from one to three months. It may be helpful to continue with maintenance injections for a whole winter.

The first injection of 0.5 cc of diluted vaccine is delivered intradermally with a 1 cc tuberculin syringe and 26G½ intradermal needle. The next dose is 0.1 cc and doses are increased by 0.1 cc until 1 cc is reached and then that amount is continued. If absolutely no local reaction occurs, 0.05 cc of the undiluted vaccine can then be administered and the progression of increases is the same as outlined for the diluted vaccine.

My criterion of a strong delayed reaction is an area of redness the size of a 25-cent piece and I make an effort never to allow the reaction to exceed that size. If the reaction is greater, then I reduce the dosage to the next lower amount and keep the dosage at that amount if it is necessary, as determined by the skin reaction. I believe that the intradermal route is the proper method to administer vaccine and to avoid serious general reactions of any kind. This method controls the potential effectiveness of the vaccine.

The patients treated received from 8 to 30 injections, depending on the progress of controlling and healing the pharyngeal lymphoid tissue. With each treatment, I also swabbed the lymphoid tissue with Lugol's Solution and glycerin,* which is not effective when used alone.

In evaluating the results of this method of therapy, I am indicating as improved those patients whose symptoms disappeared, whose reactive lymphoid tissue subsided and whose cyclic recurrence of the infection ceased. Thus 75% of the lingual tonsillitis cases improved, as did 75% of the cases with hypertrophied and swollen lateral lymphoid bands, and 100% of cases with hypertrophied, swollen, red lymphoid follicles on the posterior wall.

Certain details of therapy require some clarification. If a patient is seen at first with an acute lingual tonsillitis with purulent collections, the patient is given antibiotics. If the patient reports that such infections recur cyclically, as it did in one of our patients every six weeks for six times, the vaccine therapy is instituted. This approach holds true if the lateral bands or follicles on the posterior pharyngeal wall are badly infected.

The only other otolaryngologist whom I know who has used vaccine in a similar manner for recurring infections of pharyngeal lymphoid tissue is Dr. Karl M. Morgenstein** who has been using for approximately 20 years, first Lilly's and recently Hollister-Stier's mixed respiratory vaccines. He is of the opinion that the problem occurs more frequently in young adults and females, and that the lingual tonsils are more often involved. Dr. Morgenstein quantifies his results in the following manner: "excellent" when the lymphoid tissue undergoes involution; "very good" when the patient is rendered continually free from symptoms; "good" when there is a marked decrease in the frequency and intensity of symptoms. He believes 40% of his patients have had excellent results, another 40% very good results and the remainder good results. He further claims that the only failures he can recall are those who have discontinued the program before it was completed.

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*Iodine 12.5 gm, potassium iodine 25 gm, distilled water 25 cc, glycerin q.s. 1000 cc.

**Morgenstein, KM: Personal Communication.

Dr. Morgenstein's program was slightly different from mine, but the same principles pertain. His program consisted of a minimal test dose followed by a progressive increase in doses, given intradermally and controlled by the patient's tolerance, until the maximum dose was given once a week for eight weeks, then once every two weeks for eight doses. After that the patient received a "booster" injection every six months for a maximum period of approximately two years.

In trying to answer why and how does a vaccine control and stop these cyclic infections of the lymphoid tissue of the pharynx, I am attempting to discuss one of the most difficult issues in immunobiology and thus in medicine. To put it succinctly, I believe that the resistance of the lymphoid tissue in the pharynx against the flora of pathogens in the nasopharynx is diminished and returned to normal through the process of cell-mediated immunity or delayed hypersensitivity induced by intradermal injections of vaccine acting as the antigen. This reaction may be specific or nonspecific, but it does involve many reactions and interactions of the lymphoreticular system, without which, incidentally, life could not exist.

If one wishes to become entranced by the function of the human body, one needs only to delve into the biologic reactions involved in immunobiology. Therefore a brief review of the development of immunity in the human organism is in order. The lymphocytes are the key cells in the production of immunity be they antibodies in the form of the immunoglobulins in humoral immunity, or cell-mediated immunity, or delayed hypersensitivity in cellular immunity. The creation of immunity is helped by many agents and mechanisms such as macrophages, phagocytosis, complement, lymphokines and others. In humans all lymphocytes originate in the yolk sac in the embryo, then migrate to the bone marrow. There the lymphocytes are separated into T lymphocytes which migrate to the thymus, becoming thymic-dependent lymphocytes, and B lymphocytes which are released into the circulation to populate peripheral lymph nodes, the spleen and lymphoid tissue in the gastrointestinal tract, such as Peyer's patches. Plasma cells are fully differentiated B lymphocytes and are responsible for the production of the immunoglobulins, IgA, IgG, IgM, IgE, IgD. These are the main antibodies which confer humoral immunity.

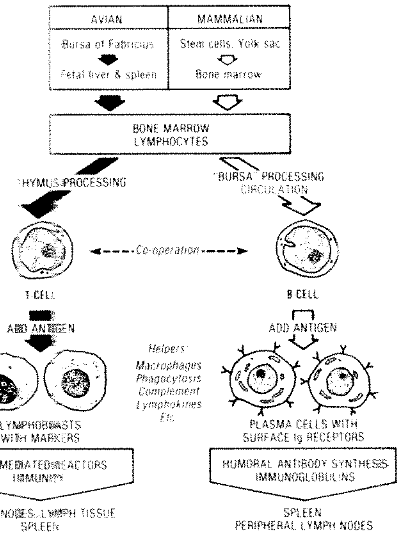

Fig. 1. Processing T and B cells for elaboration of cell-mediated and humoral immunities.

The T cells or thymic-dependent lymphocytes are the effectors of cell-mediated immunity. The T and B cells cooperate with each other biologically, and as stated before, the T cells are dependent on many other biologic factors in the elaboration of cellular immunity on antigenic stimulation. The precise manner in which this is accomplished is not yet fully understood (Fig. 1).

To appreciate this process more clearly, it is helpful to understand the relationship of these immunologic cells to lymphoid tissue. The lymphoid tissue of the faucial and lingual tonsils differ from lymph nodes only in that they do not have capsules and afferent lymphatic vessels. The lymph nodes have afferent and efferent lymph vessels, which permit the constant circulation of lymphocytes, and peripheral cortical,

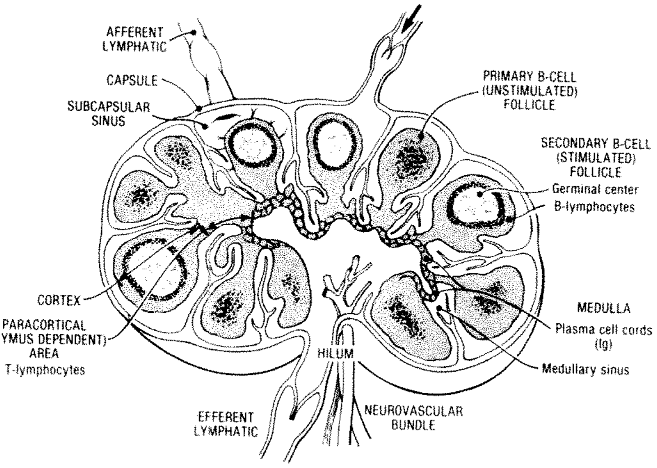

Fig. 2. Human lymph node in relation to immunity.

paracortical, and central medullary areas. In the paracortical area are located multitudes of lymphocytes which are T thymic-dependent cells. In the cortical area are primary lymphoid follicles and also germinal centers which contain B cells that have been activated. Cords of B cells enter the medulla and these are mature plasma cells, responsible for the production of the immunoglobulins (Fig. 2).

Thus, as I evaluate the clinical picture, the T or thymic-dependent cells were involved in the process which improved the resistance of the lymphoid tissue of the pharynx in the patients who overcame their tendency to cyclic infections. The cell-mediated immunity was instigated by carefully controlled intradermal injections of small doses of mixed bacterial vaccines which acted as antigens.

There have been developed recently sophisticated methods of detecting activated T lymphocyte cells participating in the process of creating cell-mediated immunity. The determination of markers on the surface of the lymphocytes is one such method.[17]

A tremendous amount of information and knowledge has been gathered in immunobiology. The problem now is to piece all this together in a logical, biological order to explain the exact way that immunity is conferred, how antigen-antibody reactions cause disease, how the rejection of homograft tissues occurs, and how neoplastic cells are biologically controlled and how control is lost and cancer develops. I feel assured that all this will happen in the not-too-distant future, and that the discoveries of antibiotics and corticosteroids will have receded in importance by that time.

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FIFTH BRITISH ACADEMIC CONFERENCE IN OTOLARYNGOLOGY

The Fifth British Academic Conference in Otolaryngology will be held July 22-27, 1979, at the University of Birmingham (U.K.). Master will be Sir Geoffrey Bateman, MA, FRCS. This conference has academic and scientific programs with distinguished international contributors to discuss a wide range of modern developments within the specialty.

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Ann Otol 87:1978

HYPERSENSITIVITY PROBLEMS IN OTORHINOLARYNGOLOGY

RUSSELL I. WILLIAMS, MD, FACS

CHEYENNE, WYOMING

The average otolaryngologist is confronted with allergic problems in well over 50% of his patients. It would seem imperative that he either recognize the problem and be able to instigate appropriate therapy himself or refer the patient to someone who can. In the latter case, he should have a basic knowledge which would allow him to evaluate adequately the therapy provided.

The otorhinolaryngologist is confronted with allergic problems in well over 50% of his patients. The majority of these have allergic symptoms of major clinical importance. It is therefore mandatory that the physician has a basic knowledge of allergy in order to diagnose adequately and instigate appropriate therapy himself or refer the patient to a qualified colleague. In the latter case, he should have sufficient knowledge of allergy to enable him to evaluate the therapy provided.

These patients deserve more than routine treatment with antihistamines. The excessive use of intranasal medication and the careless use of corticosteroids are both to be condemned. Most of the problems are referable to the nose, accessory sinuses, throat, larynx, ears and eyes. One could write a book about allergic headache, the most common complaint. Headache is followed closely by nasal stuffiness on one or both sides, which may occur shortly after retiring, continue all night and into the next day. The next most common complaint is nasal discharge, which may be anterior or, more frequently, posterior. It may be mucoid, mucopurulent or purulent. A thin, profuse mucoid anterior nasal discharge suggests food hypersensitivity.

Sneezing is a frequent complaint. It may be upon arising, seasonal or perennial, and it may occur indoors or outdoors. Sneezing upon arising is the result of the accumulated allergic insult of the previous 24 hours. Seasonal sneezing suggests a seasonal antigen, such as trees, grass or weeds. Perennial sneezing suggests perennial antigens, such as dust, molds, animal emanations, etc. If sneezing occurs during or immediately after meals, one must think of foods as a causative factor.

The nasal smear and culture of the nasal discharge, as suggested by Goldman,[1] provide an accurate method of diagnosis and indicate therapy.

Nasal polyps are seen frequently. They are usually of allergic or of dual etiology (allergy plus infection). There is sufficient evidence to indicate that patients with nasal polyps invariably have an allergic diathesis or suffer with disorders considered to be allergic in origin.[2] Nasal polyps usually originate in the mucosal lining of the ethmoid, sphenoid and maxillary sinuses. When they are of sufficient size to produce obstruction, secondary infection is invariably present. Nasal polyps may be a real problem in the salicylate (aspirin) sensitive individual. Salicylates are also found in foods, flavorings, beverages and drugs. When a patient has nasal polyps, salicylates must always be taken into consideration since they are widely represented in the foods we eat. The problem, of course, is that polypectomy and the usual allergic therapy may be of little help in the management unless the patients are placed on a salicylate-free diet.[3] Nasal polyps do not lend themselves to any single form of therapy. Immunotherapy, plus adequate antibiotic therapy, should always be

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instigated prior to and following any surgical procedure on an allergic individual.

Throat symptoms include nasal and associated ear problems referable to disturbances in the function of the eustachian tube as well as collection and drying of secretions on the mucosa of the posterior walls of the pharynx.

The buccal mucosa, uvula and the anterior pillars may reveal ulcerations, which suggest food intolerance. Analysis of nasopharyngeal secretions will be most rewarding in instigation of proper therapy.

The larynx is the gateway to the lungs and their first line of defense. Most allergic reactions in this area are in the form of edema of the epiglottis, the arytenoids or the contact surfaces of the vocal cords. Hypersecretions from the nose and accessory sinuses collect in the pyriform sinuses and spill over into the trachea, creating real problems in the very young and in the aged.

Allergic manifestations in the ear may be divided into the external, middle and inner ear. The external manifestations are fissures of the concha, with or without ulceration. Itching of the external auditory canal may represent a mild-to-severe external otitis or it may be referred directly from the nasopharynx, which suggests a food intolerance. Ulceration, discharge and pain in the external canal represent a more severe form of external otitis, which may be complicated by bacterial invasion.

One should not overlook such conditions as malignant external otitis, which may have manifestations quite similar to benign external otitis in its early stages.

In the middle ear, effusion frequently has allergic ramifications sometimes associated with autoimmune disease. Draper[4] has made a most revealing study of this condition. His conclusions deal with the allergic aspect. The endocrine factors (thyroid function, autoimmune and deficiency diseases) must be considered in the differential diagnosis of serous otitis with effusion.

Allergic manifestations of the inner ear usually lead off with a sensation of fullness accompanied by vertigo, tinnitus and/or sensorineural hearing loss. Pulec,[5] in his study of Ménière's disease, concluded that approximately 14% of the cases were of allergic origin. Goodhill[6] felt that between 15 and 20% of the Ménière's syndrome patients had an allergic etiology. Vertigo may be transient or constant (from a few minutes, to hours, to days). Among the most common excitants are yeast, milk and antibiotic sensitivity.[7]

Sensorineural hearing loss, showing periods of fluctuation, deserves a most careful evaluation.[8-10]

The eyelids may show evidence of irritation from nail polish, mascara and atmospheric contaminants. The allergic reaction may be edema of the upper or lower lid, one or both eyes, secondary to inhalants, but more often due to foods. Irritation of the conjunctiva is seen frequently in the height of the hay fever season, at any time when foods act as inhalants, or from direct or indirect exposure to animal danders, sometimes being transferred by the hand to the eye.

In perennial nasal allergy, symptoms are produced by inhalants, foods and chemicals. The inhalant antigens include house dust (the most common), the mite and the molds or fungi, which are many and varied. The most important major molds are *Alternaria* and *Hormodendrum*, which head the list, followed by *Cephalosporium*, *Mucor*, *Penicillium*, *Aspergillus*, *Pullularia* and others. Feathers of duck, goose and chicken are etiological agents, but they may have a dual purpose, since they play host to the production of molds.

Danders such as dog, horse, cat, cow, hog, rat, mice, guinea pig, parrot and others are to be considered as they are incriminated by the history.

Food additives, chemicals, insecticides and antibiotics are playing an ever-increasing role, as well as the fumes of automobile exhaust, smoke from fires, smog, plant emanations of volatile oils (terpenes) and particularly the ubiquitous plastics, some of which literally breathe odors and irritants.

Foods may act as ingestants or inhalants. For instance, the cereal flours acting as inhalants when used in preparation of bread are the cause of "baker's asthma."

Symptoms of food hypersensitivity or intolerance are many and varied.[11] There are two basic types of food allergy: fixed and cyclic. A fixed food allergy is one in which symptoms occur following each ingestion of that food regardless of the length of time the food has been omitted from the diet. It constitutes about 5% of all food allergies. In cyclic food allergy, frequency of usage of a food tends toward sensitization or intolerance and omission tends toward tolerance.[12]

Seasonal variations in symptoms are noted with perennial antigens such as dust and molds, but they will peak at various times of the year. The dust season usually begins with the turning on of the furnaces in the fall. The season reaches it peak in January, beginning to slack off from then to March, April and May to its lowest level in June, July and August. Molds or fungi peak in August, escalating with ragweed and other fall pollens.

Pollens will vary with the different areas of the country. The tree season begins as early as late December and continues through February and March. In the Rocky Mountain area, for example, tree pollens are still present in some areas as late as early May. The grass season begins in May and June. Plantain comes in in the eastern part of the country the first three weeks of June and in the higher elevations it may continue well into July, depending upon the altitude. Other weeds, such as the pigweeds, Russian thistle and kochia, usually begin pollinating early in July and reach their peak with kochia the latter part of July. Lambsquarters pollinates in late August and early September. Ragweed will vary in different areas, but usually occurs from early August into late October or early November. In the Rocky Mountain area, sage pollen is a real problem, usually pollinating about the same time as ragweed. Ragweed is not profuse in the Rocky Mountain area, but is of considerable importance in management of seasonal pollinosis. Burweed marshelder and lambsquarters usually peak in late August, as do the molds of *Alternaria, Hormodendrum* or *Cladiosporium.*

In many areas of the country the miller moth (silk) becomes a factor early in June and again in September.

There are other pollens which are of importance to a certain percentage of the population and one should become familiar with the seasonal pollens of his particular area and learn to test and treat accordingly.[13]

In allergy, the leading diagnostic tool is the history. A good history requires an in-depth knowledge of the symptoms that may be produced in different individuals by different antigens: Are they seasonal or perennial? What time of day do they occur? It it early morning, upon retiring? Indoors or outdoors? On a windy day? After a rain? In the cool of the evening? The history, regardless of the time spent compiling it and the experience of the physician, is never totally accurate nor complete.

Skin tests are made by scratch, prick, intradermal or superficial intracutaneous. Skin tests for inhalants, properly applied and properly interpreted, are highly accurate. Skin tests for foods are not reliable.

The Food Challenge Test, the Provocative Subcutaneous and Intracutaneous Tests, the Food Fasting Test, the Cytotoxic Test and the RAST Test are methods of diagnosing food allergy.

Serial dilution 1:5 superficial, intracutaneous, antigen titration was developed by Rinkel.[14] This is a method of determining the degree of sensitivity to a specific antigen by the whealing response of the skin. It is performed by injection of a weak, nonreacting dilution of an antigen, applying successively stronger test dilutions until a reaction occurs, which is termed the endpoint of reaction. This, in turn, will be followed by a 2 mm increase in the size of the wheal as the next stronger test dilution is applied, thus establishing progressive whealing. This increase will be consistent through three or four dilutions. The first reacting test dilution is the endpoint of reaction. It is this dilution at which treatment can be started safely within a close therapeutic range. Approximately 72% of the tests applied will produce an abrupt endpoint of reaction and these can be interpreted very easily. The remaining 28% may show bizarre reactions.[14]

Using this method, it is possible after three to five injections to show clinical improvement. For those who do not show improvement, one must review the history, review the antigens used and retest the patient to see if he is being treated at the proper degree of sensitivity demonstrated by the skin response. If he is not, then proper therapy is instigated.[15]

The optimal dose is described as that dose which gives the highest degree of relief for a period of time, which may vary from 3 to 21 days. The amount may vary from 0.07 ml of the endpoint dilution to 150 times that amount. This dose is found only by finding the endpoint of reaction and following a recommended, escalated dose schedule until this degree of relief is obtained.

Recent advances in knowledge of the immunoglobulins, especially IgE and IgG are of value and will become increasingly significant as experience in technique and interpretation accumulate. Specific IgE (RAST) test will be increasingly more important in identifying the relevant antigens. The total IgE (PRIST) test will be of value in screening the allergic individual. These tests are limited to date in the study of food problems for two reasons: there are not enough food antigens presently available and a large number of food allergies or intolerances are not IgE-mediated.

In summary, the hypersensitivity problems encountered by an otorhinolaryngologist today are numerous and basic and, in many instances, of major clinical importance. It is therefore mandatory that the physician has a basic, in-depth knowledge of allergy in order to diagnose adequately and instigate proper therapy. If he does not care to do his own allergy work, it is imperative that he understand allergic mechanisms so that he is able to predict and/or demand results consistent with good allergic practice from the colleague to whom he refers his patient.

Many allergic patients, if seen early enough, will respond well to proper allergy management. Surgical patients who have an underlying allergy will have consistently better results if the allergy is treated adequately preoperatively and continued postoperatively.

The future otorhinolaryngologist who incorporates management of hypersensitivity problems into his practice will be gratified by his successful results.

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NINCDS NOTES*

OTOLARYNGOLOGIST JOINS STAFF

Dr. Rolf Fredric Ulvestad, an otolaryngologist from the University of Minnesota, has joined the Communicative Disorders Program, and is responsible for NINCDS grant and contract support research activities in clinical otolaryngology. He is also a consultant to the NIH Clinical Center, collaborating on otolaryngological aspects of Clinical Center studies.

DIABETIC NEUROPATHY PAMPHLETS AVAILABLE

A new pamphlet, "The Diabetic Neuropathies: A Scientific Guide for Health Practitioners," is available from the NINCDS free of charge. Written for health care practitioners, the pamphlet describes the four major types of diabetic neuropathy and summarizes current understanding of the disorder's pathogenesis and methods of treatment.

Physicians are urged to inform patients of a free companion pamphlet, "The Diabetic Neuropathies," intended for patients and their families. This pamphlet describes diabetic neuropathy symptoms and their causes in layman's terms, and suggests practical methods for coping with the disorder.

Pamphlets may be obtained from NINCDS, Office of Scientific and Health Reports, Building 31, Room 8A 06, Bethesda, MD 20014.

GRANTS SOUGHT FOR NEURONAL INTERACTIONS

The NINCDS Fundamental Neurosciences Program is encouraging applications for research grants on local neuronal interaction. Such research may lead to a better understanding of basic neurobiological mechanisms, as well as "higher" brain functions, such as learning, memory, or complex behavior.

DEPUTY DIRECTOR'S APPOINTMENT ANNOUNCED

NINCDS Director Dr. Donald B. Tower has announced the appointment of Dr. Murray Goldstein as Deputy Director for Neurological Sciences and Disorders. Dr. Goldstein, who has been Director of the NINCDS Stroke and Trauma Program will continue to serve as Acting Director of that program until a replacement is recruited.

In his Deputy Director's post, Dr. Goldstein will be a principal advisor to Dr. Tower regarding the Institute's objectives and policies, and its allocation of financial resources for programs within the neurological sciences and disorders.

REMINDER TO ACKNOWLEDGE SUPPORT

The NINCDS would like to stress to grantees the importance of acknowledging grant support in articles for the public concerning their research. The Institute is constantly striving for a greater public awareness of the kinds of research supported or conducted by the Institute, and for a better understanding of the role of the Institute and its grantees in the total medical and scientific research communities.

ADVISORY COUNCIL MEMBERS APPOINTED

Three new members have joined the Institute's National Advisory Neurological and Communicative Disorders and Stroke Council for four-year terms. They are Franklin S. Cooper, former President and currently Associate Research Director of Haskins Laboratory, New Haven, Conn.; Dr. Sidney Goldring, Professor and Head, Department of Neurosurgery, Washington University, St. Louis, Mo; and Mrs. Jenniger Jones Simon, actress and former member of the Commission on Huntington's Disease and its Consequences.

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LARYNGOCELE AND SACCULAR CYSTS

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The symptoms, endoscopic findings, treatment and results of 46 patients with laryngoceles and saccular cysts are presented. Thirty-four were adults; 12 were infants and children under three years of age. Twenty-two adults had anterior saccular cysts, nine had lateral saccular cysts, three had laryngoceles. Ten infants and children had saccular cysts; two had laryngoceles. A laryngocele is an abnormal dilatation of the saccule which communicates with the lumen of the larynx, fills with air but on occasion may be temporarily distended with mucus; laryngoceles may be congenital or acquired. A saccular cyst is a mucus-filled dilatation of the saccule which does not communicate with the laryngeal lumen; saccular cysts are classified as lateral or anterior. Laryngoceles and saccular cysts represent abnormalities of the laryngeal saccule; a developmental spectrum exists among the normal saccule, large saccule, laryngocele and saccular cyst. The treatment of saccular cysts in infants and children is primarily repeated aspiration. In adults, symptomatic laryngoceles and large lateral saccular cysts are treated by an external approach; endoscopic aspiration and unroofing of small lateral saccular cysts is sometimes adequate and is attempted first. Anterior saccular cysts are treated by endoscopic excision biopsy. Carcinoma of the larynx may be found in association with a laryngocele or saccular cyst and must be diligently searched for by biopsies in the region of the saccular orifice. A smooth mass involving the area of the false vocal cord and aryepiglottic fold cannot be assumed to be a lateral saccular cyst; biopsies of the ventricle and saccule and deep incisional biopsies of the mass are indicated to rule out a carcinoma originating in the ventricle or saccule.

The laryngeal ventricle was mentioned first by Galen[1] in the second century A.D. In 1741, Morgagni[2] described the ventricle in detail but it was not until 1837 that Hilton[3] reported the anatomy of the saccule.

The first air-containing "tumors" of the neck were reported in 1829 by Larrey,[4] surgeon to Napoleon's army in Egypt. He called them "goîtres aeriennes," and found them to be frequent among the blind criers who called the faithful to prayer from the minarets. Apparently unaware of Larrey's description, Virchow[5] introduced the term laryngocele in 1867 to describe an air-filled dilatation of the saccule.

In 1881, Abercrombie[6] described a laryngeal cyst in a newborn and used the term congenital cyst. The first report of such a cyst in vivo was made by Marx[7] in 1928. De Santo et al[8] discussed saccular cysts in detail in 1970.

This brief historical review describes the development of terminology for the anatomy and pathology of the laryngeal ventricle and saccule over 18 centuries by scholars of different languages and training; understandably there is a lack of a consistent terminology and precise definitions which are agreed upon by all authors. The data and conclusions of this study are presented to clarify the anatomic and etiologic relationships which exist among these similar conditions.

Anatomy. The laryngeal *ventricle* (ventriculus laryngis Morgagnii; laryn-

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†Dr. Paul Holinger died March 26, 1978.

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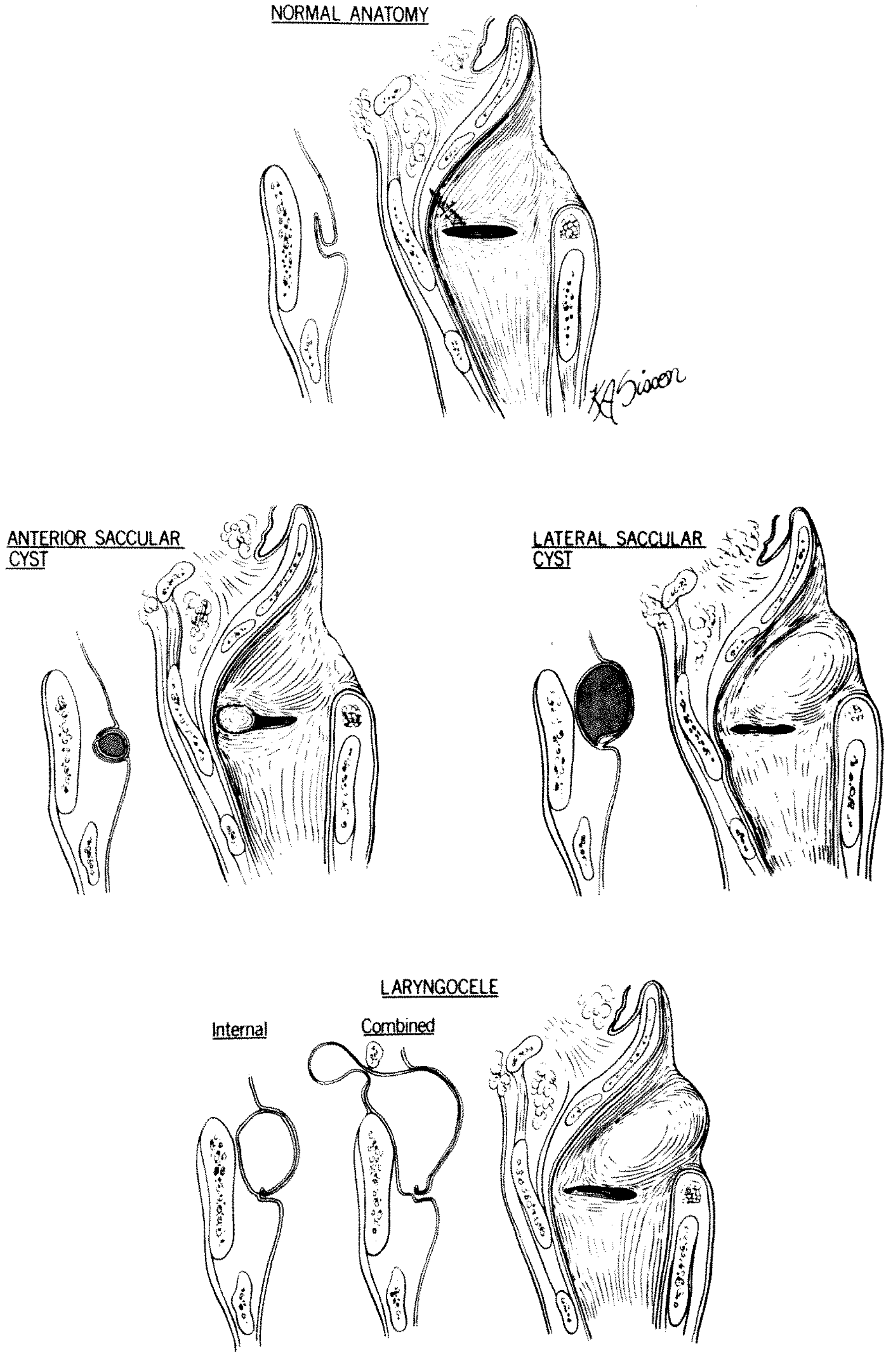

Fig. 1. Coronal and sagittal sections demonstrating the anatomy and pathology of the laryngeal saccule and ventricle. Schematic coronal sections are taken through the anterior larynx at the level of the saccular orifice.

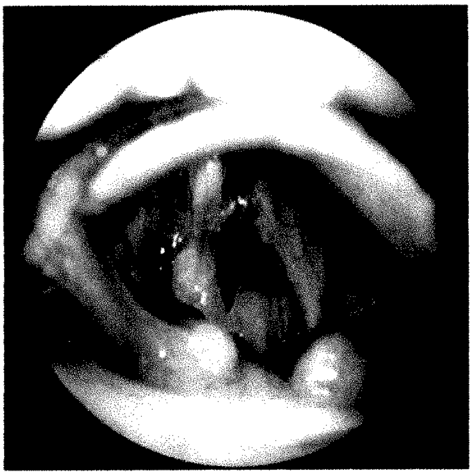

Fig. 2. Indirect (mirror) view of a left anterior saccular cyst in an adult. The cyst rests on the superior surface of the true vocal cord displacing it inferiorly and damping the vibration to produce symptoms of hoarseness and a persistent desire to clear the throat.

geal sinus) is a fusiform fossa bounded by the true vocal cord (vocal fold) and the false vocal cord (ventricular fold). The anterior part of the roof of the ventricle leads up into a cecal pouch of mucous membrane called the saccule.

The laryngeal saccule (appendix ventriculi laryngis; sacculus laryngis) rises vertically between the false vocal cord, the base of the epiglottis, and the inner surface of the thyroid cartilage (Fig. 1). On the surface of its mucous membrane are the openings of 60-70 mucous glands. Medial and lateral to the saccule are delicate muscles which compress it to express its secretions upon the vocal cords. At the orifice of the saccule is the ventriculo-saccular fold, an anterior crescentic fold of mucous membrane which probably serves to help store mucus and direct it posteromedially to lubricate the surface of the vocal cord.[9]

Pathology. A *laryngocele* is an abnormal dilatation or hernia of the saccule (Fig. 1). It communicates with the lumen of the larynx and is air-filled but on occasion may be temporarily distended with mucus. An internal laryngocele is confined to the interior of the larynx and extends posterosuperiorly into the area of the false vocal cord and aryepiglottic fold. An external laryngocele extends cephalad to protrude laterally into the neck through the opening in the thyrohyoid membrane for the superior laryngeal nerve and vessels. When an external laryngocele is combined with a symptomatic dilation of the internal portion it is termed a combined laryngocele.

A *saccular cyst* (congenital cyst of the larynx, laryngeal mucocele, saccular mucocele) is a mucus-filled dilatation of the saccule which does not communicate with the laryngeal lumen; saccular cysts are distinctly submucosal and are covered with normal mucous membrane.[8]

There are two types of saccular cysts. The *lateral saccular cyst* extends posterosuperiorly into the false vocal cord and aryepiglottic fold from its origin at the nonpatent orifice of the saccule (Fig. 1). The *anterior saccular cyst* extends medially and posteriorly from its origin at the nonpatent orifice of the saccule to protrude into the laryngeal lumen from between the true and false vocal cords (Figs. 1 and 2).

Laryngoceles and saccular cysts are similar in that both represent an abnormal dilatation of the laryngeal saccule. The saccular cyst is distinguished from the laryngocele in that its lumen is isolated from the interior of the larynx and does not contain air.

METHODS AND MATERIALS

The symptoms, endoscopic findings, treatment and results of 46 patients with laryngoceles and saccular cysts observed between January 1, 1960, and December 31, 1977, were reviewed. Thirty-four were adults and 12 were infants and children under three years of age. Diagnosis was confirmed by direct endoscopic examination of every patient.

RESULTS

INFANTS AND CHILDREN

Saccular Cysts. Ten infants and children had saccular cysts (Fig. 3). Six were lateral saccular cysts; four were anterior saccular cysts. In six the cyst was on the right; in four on the left. All exhibited respiratory distress; the most constant symptom was inspiratory stri-

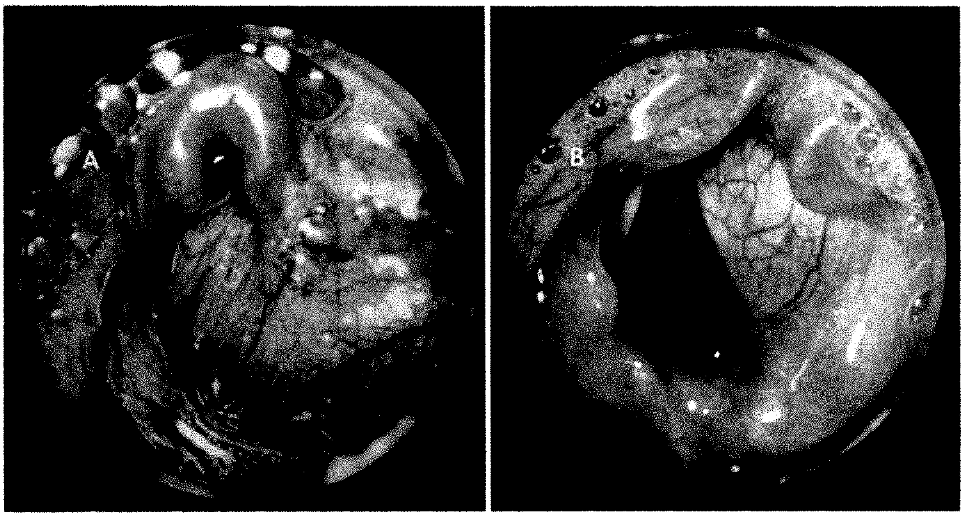

Fig. 3. A) Lateral saccular cyst seen on direct laryngoscopic examination. The congenital cyst completely obliterates the right aryepiglottic fold and the laryngeal lumen; the infant ventilates through a tracheotomy tube. The omega-shaped epiglottis is seen anteriorly. B) Direct laryngoscopic view of a large right anterior saccular cyst in a newborn bulging from between the true and false vocal cords. This congenital lesion caused constant dyspnea and an abnormal, weak cry. A portion of the normal left vocal cord is visible.

dor. Five children had severe suprasternal and intercostal retractions; three had episodes of cyanosis. Two had an inaudible cry, and two a muffled cry. Dysphagia was present in three. Associated congenital anomalies included mild laryngomalacia in one infant and bilateral vocal cord paresis in another; the paresis gradually disappeared within one year.

Seven of the ten children underwent lateral soft tissue x-rays of the neck; the cyst was apparent in all cases. Direct laryngoscopy and aspiration of the cyst was done in all ten cases; five later required endoscopic unroofing with a cup forceps. Biopsies disclosed the cyst walls to be composed of either ciliated columnar or stratified squamous epithelium. The cysts were found to contain thick, clear or cloudy mucoid secretions. Tracheotomy was necessary in six of the ten children and was required for 4 to 29 months, a mean of 17 months.

During the treatment period laryngoscopies were repeated between 1 and 14 times, a mean of 7.5 laryngoscopies on each infant. One child underwent external excision of a persistent cyst after 11 laryngoscopies; it did not recur.

Complications included the formation of granulation tissue at the base of the cyst in two children. Mild subglottic stenosis occurred in two who had undergone tracheotomy. All complications resolved without further sequelae; all were decannulated; there were no mortalities.

Laryngocele. Two children, one female and one male, had laryngoceles. The two-month-old male presented with intermittent hoarseness and dyspnea which increased with crying. The eight-month-old female had a history of a weak cry and intermittent aphonia. Direct laryngoscopy disclosed a fullness of the right false vocal cord and aryepiglottic fold in both cases; needle aspiration produced no fluid. In addition to the endoscopic appearance, the diagnosis was made on the basis of the x-ray findings and the intermittent nature of the symptoms. Symptoms gradually resolved in both cases after diagnostic laryngoscopy; no further treatment was required.

ADULTS

Of the 34 adults, 22 had anterior saccular cysts; 9 had lateral saccular cysts; 3 had laryngoceles. There were 14 males and 20 females. No adult patient was engaged in a professional or leisure activity requiring prolonged periods of increased intralaryngeal pressure.

Saccular Cysts. The 22 adults with *anterior saccular cysts* ranged in age from 32 to 74; most were diagnosed in the seventh decade. Females outnumbered males 15 to 7. The cyst was on the right in 10 patients, on the left in 12. Hoarseness was the most common symptom and was present in 20 patients. Fourteen used tobacco. Anterior saccular cysts were diagnosed and treated by endoscopic excision using cup forceps at direct laryngoscopy. Twenty patients required treatment; there were no recurrences.

The nine adults with *lateral saccular cysts* ranged in age from 29 to 78 and were most often diagnosed during the sixth decade. Four were males, five females. The left side was affected in five cases, the right in four. The presenting symptoms were hoarseness alone (5), hoarseness and dyspnea (1), hoarseness and dysphagia (1), dysphagia alone (1), and pain (1). Five smoked tobacco.

After radiologic evaluation, the lateral saccular cysts were examined by direct laryngoscopy and most were aspirated. Seven patients underwent subsequent external excision. One patient with a laryngopyocele underwent external resection following resolution of the infection. Another patient treated initially with endoscopic aspiration and biopsy was found to have tuberculous laryngitis producing the cystic enlargement of the right aryepiglottic fold. A third patient who had a cystic enlargement of the left supraglottic larynx underwent endoscopic aspiration of the cyst and multiple biopsies at each of four examinations over a two-year period. Squamous cell carcinoma was finally diagnosed and a laryngectomy was necessary.

Laryngocele. The three adults with laryngoceles ranged in age from 56 to 78; two were males, one female. All were right-sided. Presenting symptoms were sensation of throat malfunction, intermittent shortness of breath with persistent hoarseness, and episodic sensation of "swollen throat." The diagnosis was confirmed with direct laryngoscopy. All were resected through an external approach; there were no recurrences.

DISCUSSION

Unfortunately, most authors[4,5,10-15] do not discuss the precise definitions and the distinction between a large saccule and a laryngocele. This is a critical detail in determining the prevalence of laryngoceles. De Santo[10] indicates that a large saccule becomes a laryngocele when it is symptomatic and palpable. According to Keim and Livingstone[16] air sacs rising higher than the upper border of the thyroid cartilage exceed the limits of normality which Virchow[5] arbitrarily defined.

Broyles[illegible] dissected 50 fresh adult larynges and found that 75 of the 100 laryngeal saccules "extended up 6-8 mm." In 25, the depth of the cavity extended 10 mm or more, 7 of which extended greater than 15 mm. He does not mention the relationship of the saccule to the thyroid cartilage, but since the superior margin of the thyroid cartilage ala is approximately 16 mm above the superior surface of the vocal cords, a significant percentage of normal or large saccules may extend above it. In the infant, however, the saccule is relatively larger; in 25% of 22 fetal and newborn larynges the saccule was found to extend above the superior margin of the thyroid cartilage.[18]

In summary, a diagnosis of laryngocele may be made when an ectatic, dilated saccule is: 1) symptomatic, 2) palpable, 3) observed internally by indirect or direct laryngoscopy, and 4) observed radiologically or by dissection (at surgery or autopsy) to extend above the superior margin of the thyroid cartilage ala.

As noted in a previous communica-

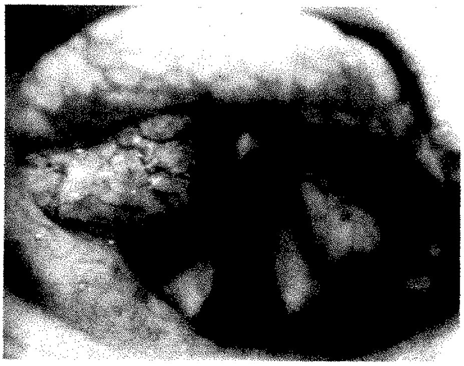

Fig. 4. Indirect (mirror) laryngoscopic view of a cystic enlargement of the right false vocal cord. Although the mass contained thick viscid fluid, the diagnosis of an internal laryngocele was made. The intermittent nature of this 62-year-old woman's hoarseness and dyspnea confirmed a communication with the interior of the larynx. When the patient coughed or talked forcefully the mass increased in size to overhang the true vocal cord. Dyspnea followed each cough as the laryngocele inflated; the glottic lumen returned to normal size as the laryngocele gradually deflated.

tion,[19] laryngoceles become clinically perceptible only when distended by air forced into them or when temporarily filled with a collection of fluid. In the latter situation it is apparent that laryngoceles and saccular cysts are often indistinguishable from each other; a fluid-filled smooth mass distending the aryepiglottic fold may be a saccular cyst or a laryngocele. While other criteria were applied in previous publications by the senior author,[20-22] for the purposes of this study, clinically perceptible enlargements of the saccule filled with fluid were considered saccular cysts; when filled with air they were classified as laryngoceles. There was one exception: fluid-filled saccular enlargements which emptied or filled with air during coughing or speech were considered laryngoceles (Fig. 4); the intermittent nature of these symptoms implies a patent saccular orifice, and therefore a laryngocele.

Less controversy surrounds the precise definition of a *saccular cyst.* A saccular cyst exists in the absence of a patent saccule orifice so the lumen does not communicate with the air column of the larynx. This leads to dilatation of the saccule which is filled with mucus rather than air.

While some authors have attempted to categorize laryngeal cysts on the basis of histological findings, Holinger and Steinmann[19] and others[8] have concluded that histologic patterns alone are not specific enough. Symptomatology, location, depth and size as determined by radiologic evaluation, laryngoscopy, palpation and surgical exploration are considerably more useful and accurate.

A *laryngopyocele* is best understood in terms of the basic anatomy and the developmental spectrum described by De Santo.[10] It is an infected (pus containing) laryngocele, saccular cyst, large saccule or saccule in which the orifice has become occluded due to the infectious process. While the term was first coined and applied to an infected laryngocele, an infected laryngocele is indistinguishable from any pus-containing saccular dilatation.

A *ductal cyst* (acquired cyst, [mucus] retention cyst), the common cyst found anywhere within the larynx, results from retention of mucus in the collecting ducts of the submucosal glands. While the literature consistently refers to duct obstruction as the genesis of many cysts, the term ductal cysts is preferred because the cysts are dilated ducts and not distended glands as is commonly thought.[8] With the exception of a few cysts having fibrous linings, all cysts which are not saccular cysts are lined with cells of the ductal type.[8] In contrast to saccular cysts, ductal cysts are usually less than 1 cm in diameter and are quite superficial within (not deep to) the mucous membrane. They are three times more common than saccular cysts; in the review of 238 cysts of the larynx by De Santo et al,[8] 180 (75%) were ductal while 57 (24%) were classified as saccular derivatives. Ductal cysts are not included in the present study.

Since ductal cysts may form from the ducts of mucous glands which populate the saccule, it is not unlikely that these cysts may enlarge to present with the appearance of an anterior saccular cyst.

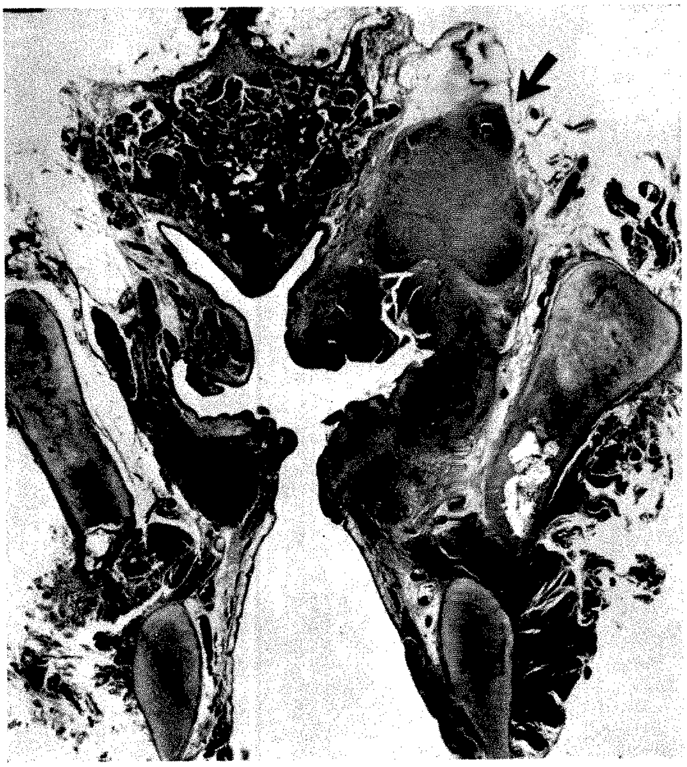

Fig. 5. Coronal section of a laryngectomy specimen harboring a squamous cell carcinoma in the region normally occupied by the saccule. The mucosa of the true and false vocal cords is intact; endoscopic examination revealed only a persistent fullness of the left false vocal cord. Three procedures and a deep biopsy were required to finally obtain a definitive diagnosis of this insidious lesion. The biopsy site is seen on the roof of the ventricle in this section. (Reproduced by kind permission of the author and publisher: Tucker GF Jr: A histological method for the study of the spread of carcinoma within the larynx. Ann Otol Rhinol Laryngol 70:910-922, 1961.

ETIOLOGY

The pathogenesis of *laryngoceles* remains controversial. The extent to which congenital or acquired factors may be implicated must be assessed in each individual case. A congenital variation may be the only cause in some cases; the laryngoceles observed in newborns are certainly congenital. Large saccules and laryngoceles may represent atavistic remnants corresponding to the lateral air sacs of higher anthropoid apes. In some specimens the size of these sacs is enormous and after perforating the thyrohyoid membrane reach the subclavicular or even the axillary spaces; the phylogenetic aspects of the condition have been discussed.[17,23]

In adults a congenital defect or anatomic variation of the saccule may be implicated to greater or lesser degrees and acquired factors may be partially or completely responsible. One might postulate that an abnormally large saccule or one with a congenital defect or weakness may predispose toward laryngocele formation and slowly enlarge until becoming symptomatic. The apparent, increased incidence of laryngoceles in patients with carcinoma of the larynx[12-14,19] and in patients whose occupations or hobbies involve prolonged periods of increased pressure within the laryngeal lumen,[4,15,24] suggest that acquired factors contribute to laryngocele formation in some cases.

Stell and Maran[11] have reported two patients whose laryngoceles appeared "at the same time as the patient took up trumpet playing," thus merely bringing an already existing laryngocele or large saccule to the patients' notice; they reported similar cases in which laryngoceles were first noted after coughing and summarily discounted acquired factors in the formation of laryngoceles. However, these cases are in the minority and while laryngoceles and anatomic variations in the size of the saccules may become apparent only under appropriate conditions, there are certainly some cases of presumably normal saccules which enlarge to form laryngoceles after years of prolonged increase in intralaryngeal pressure. The original description of laryngoceles by Larrey[4] supports this concept as does the experience of Stephani and Tarab[24] who made radiologic examinations of 26 wind instrument players and found laryngoceles in 100%; 11 were symptomatic. Furthermore, it is difficult to brush off as an incidental finding MacFie's observations of laryngoceles in 56% of 94 wind instrument bandsmen.[15]

Thus a spectrum exists: a laryngocele may be purely congenital (as in the newborn), represent a congenital defect made apparent or exacerbated by habitual, increased intralaryngeal pressure, or at the other extreme perhaps rarely be acquired solely on the basis of prolonged increased intralaryngeal pressure.

Increased intralaryngeal (ventricular) pressure is brought about by many activities (e.g., lifting, defecating, etc.) involving a strain which requires fixing the diaphragm in forced expiration against the closed larynx: a Valsalva maneuver. This increases not only subglottic pressure but ventricular pressure as well. Lindsay[25] showed that with increased physical exertion there appears to be more firm apposition of the false cords than of the true cords. Negus[23] felt that the false vocal cords function as a one-way valve in addition to their sphincteric action in preventing the egress of air. While Lindsay's study brings into question the valvular nature of the false cords there is little question that false cords remain competent to allow the considerable force of the increased pressure to be exerted at the ventricular level.

Increased intralaryngeal (ventricular) pressure is also caused by activities requiring a modified Valsalva maneuver in which intrathoracic pressure, increased during expiration, is fixed against the lips. This mechanism causes increased ventricular pressure in wind instrument players.

Saccular cysts may be congenital or acquired. When congenital, a saccular cyst may form as the result of simple atresia of the saccular orifice, a process commonly encountered as a cause of congenital abnormality;[26] saccular cysts apparent at birth are explained on this basis. Which type of saccular cyst is formed may depend on the point at which the atresia forms or the size of the saccule; it seems likely that anterior saccular cysts arise from small saccules, lateral saccular cysts from large ones. Acquired saccular cysts may be due to occlusion of the saccular orifice by trauma, neoplasia, or inflammatory conditions or the resulting fibrosis.

TREATMENT

Infants and Children. Needle aspiration is the initial treatment of *saccular cysts* in infants; the diagnosis is established and frequently no further surgical intervention is necessary. Recurrence may necessitate repeat aspiration; if the cyst continues to recur it is unroofed and the frayed edges of redundant mucosa removed with a laryngeal cup forceps. Temporary tracheotomy may be required. The external approach is avoided in infants. In the rare cases of a true *laryngocele* in the newborn, unroofing the superior extent of the lesion has proved effective; this is accomplished endoscopically using a small cup forceps.

Adults. Anterior saccular cysts are treated by complete cup forceps removal (excision biopsy) at the time of diagnostic direct laryngoscopy.

Small *lateral saccular cysts* are successfully managed endoscopically. The orifice of the saccule is biopsied. Needle aspiration confirms the diagnosis and is sometimes adequate. Endoscopic unroofing with a cup forceps is recommended.

Laryngoceles, large cysts and recurrent cysts are treated by submucous resection through an external approach after thorough preoperative evaluation and biopsies. The procedure described by Yarington and Frazer[27] adheres to the principles of adequate exposure for complete excision with minimal intralaryngeal trauma. Through a horizontal skin incision at the superior margin of the thyroid cartilage, the strap muscles are retracted and the thyrohyoid membrane identified. The thyrohyoid membrane is incised along the superior margin of the thyroid cartilage; blunt dissection exposes the cyst which bulges into view from its location in the paraglottic space. If the cyst or laryngocele protrudes into the neck it is followed through the thyrohyoid membrane over the superior margin of the thyroid cartilage. Decompression of the lesion facilitates the dissection. Care is taken to identify and preserve the superior laryngeal nerve; Johnston[28] first emphasized this point and Ward et al[29] have detailed the morbidity which results from surgical trauma to the nerve. The lesion is dissected out, the base ligated and the specimen removed. It is rarely necessary to remove a portion of the thyroid cartilage. Thyrotomy and entry into the laryngeal lumen is to be avoided. Tracheotomy is usually performed as a prelude to the external resection.

Laryngocele, Saccular Cyst and Cancer. While the concomitant occurrence of laryngocele (or saccular cyst) and carcinoma of the larynx is a well documented phenomenon,[12-14,30-34] the prevalence and the precise nature of this relationship lacks clear definition. In most cases, laryngocele formation is likely due to the carcinoma; the mechanism probably involves a valve-like mechanical obstruction of the saccule by the malignant process with resulting saccular dilatation.

Considerable controversy surrounds the incidence of laryngoceles in patients with laryngeal carcinoma. Meda[13] reported a 1-2% incidence of laryngocele in laryngeal cancer. Pietrantoni et al[14] studied patients who underwent laryngectomy for carcinoma. Using preoperative radiological findings they concluded that 53 (6.18%) of 857 patients had laryngoceles; 87% were bilateral (although the neoplasm was not necessarily bilateral). The criteria for diagnosis of laryngocele are not recorded. Stell and Maran[11] report that Gerard-Marchant et al[30] found external laryngoceles in 16% of laryngectomy specimens operated for laryngeal carcinoma but in only 2% of the specimens from patients with carcinoma of the pyriform sinus. Micheau et al[31] have recently updated this series. They report 2% of 360 pharyngolaryngectomy specimens which had no laryngeal invasion by tumor were found to have external laryngoceles. Among 546 total laryngectomy specimens, there was an 18% incidence of external laryngoceles. The authors conclude that these findings confirm the role of endolaryngeal cancer in the development of laryngoceles.

The occurrence of a laryngocele, saccular cyst, or even a laryngopyocele in an adult should arouse suspicion of an associated laryngeal neoplasm; the literature is resplendent with case reports of this occurrence. The experiences of Lund[32] and Harrison[12] are typical in this regard: they report cases in which a laryngocele or saccular cyst was resected only to have a large laryngeal tumor become apparent a short time later.

Another point to consider is the evaluation of a lesion which at indirect laryngoscopy appears to be a lateral saccular cyst.[17,31] A thorough radiologic and endoscopic evaluation is undertaken to rule out an underlying carcinoma which may originate in the saccule, within the confines of the paraglottic space. Such a lesion may progress to a significant bulk before presenting in the laryngeal lumen through the ventricle or by ulcerating through the false vocal cord. Only a smooth, benign-appearing mass may be evident, enlarging the false vocal cord and aryepiglottic fold and having the typical appearance of a lateral saccular cyst. A computerized tomographic scan is the most useful radiologic study; accurate diagnosis may necessitate deep incisional biopsies of the suspicious area as well as careful inspection and biopsies of the ventricle and saccule.

Meda[13] gives credit to Cova[34] for a final consideration with regard to laryngocele and cancer. His concept is that a laryngocele discovered during the radiologic evaluation of a carcinoma of the larynx implies infiltration of the ventricle by the carcinoma. The laryngocele may therefore be of significance in determining the extent of the lesion.

Oncocytoma. The oncocytic cyst (granular oxyphilic columnar lined cyst, cystadenoma of the larynx) should be mentioned since it comprises 35% of saccular cysts.[8] Its location and behavior is not different from nonoxyphilic cysts; the oxyphilic cyst is therefore considered a histologic variant without known clinical significance although the pathogenesis remains undetermined.[8]

Oncocytic lesions of the larynx are frequently compared to oncocytomas and Warthin's tumor of the parotid gland.[35-37] Oncocytes from both locations demonstrate identical electron microscopic findings of cells packed with mitochondria and active oxidative enzymes, findings which do not corroborate a degenerative process as the cause.[36] Many authors[36,38,39] believe oncocytic cysts in various locations represent only a small portion of a morphologic range of oncocytic change. Allegra[38] uses the term Warthin's disease and postulates a hypersensitivity reaction as the etiology. He and others[39] describe specific ranges or stages in the development of oncocytic lesions in general. All agree that oncocytic lesions are considered lesions of epithelial hyperplasia and metaplasia rather than true neoplasms.[39]

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EVALUATION OF RANDOMIZED PREOPERATIVE AND POSTOPERATIVE RADIATION THERAPY FOR SUPRAGLOTTIC CARCINOMA

PRELIMINARY REPORT

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One hundred and ten patients with supraglottic squamous cell carcinoma have been randomized for preoperative radiation therapy and surgery versus surgery and postoperative radiation therapy. Data have been analyzed on 94 patients in this preliminary report. The differences between the two groups with respect to local control and survival are not statistically significant at this time. Additional accrual and continued follow-up are necessary in order to make a more definite treatment comparison.

Patients with early squamous cell carcinoma of the supraglottic portion of the larynx (Stage I and II) are successfully treated with irradiation or surgery. Radiation therapy or surgery for patients with more advanced squamous cell carcinoma of the supraglottic larynx frequently fails to control the neoplasm in the primary site and the cervical lymphatic bed.[1,2] Combined therapy with irradiation and surgery appears to provide in consecutive series better local control and five-year survival rates than either form of treatment alone. Apparent improved local control and survival have been demonstrated with treatment plans in which the radiation therapy is given preoperatively and with treatment plans in which the radiation therapy is given postoperatively.[3] Although local control is enhanced by combination therapy, salvage by a second procedure after primary surgery or irradiation alone is not as successful.[2]

The incidence of distant metastasis in patients with supraglottic carcinoma is 13% if disease above the clavicles is controlled and is 20% if carcinoma persists above the clavicles.[3]

In January of 1973 the Radiation Therapy Oncology Group initiated a study of the treatment of patients with advanced carcinoma of the oral cavity, oropharynx, supraglottic larynx and hypopharynx with preoperative radiation therapy and surgery versus surgery and postoperative radiation therapy to assess local control, site of first failure, distant metastasis, survival, complications of therapy, functional status of the patient after therapy, and cause of death. The randomization of patients with oral cavity and oropharyngeal carcinomas includes definitive radiation therapy with surgical rescue in 90 days. On September 23, 1977, 287 patients had been entered into the study. The largest group of these patients had supraglottic carcinomas, and the pre-

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This report is based on a study of the Radiation Therapy Oncology Group supported through Radiation Therapy Oncology Group Headquarters grant number CA 21661.

Presented at the meeting of the American Laryngological Association, Palm Beach, Florida, April 22-23, 1978.

liminary results in these 110 patients are the basis of this report.

METHODS AND MATERIALS

Sixteen members of the Radiation Therapy Oncology Group participated in the study.* Patients with T_2, T_3 or T_4 biopsy proven squamous cell carcinoma of the supraglottic larynx are eligible for the study. The supraglottic larynx includes the epiglottis, ventricular bands and aryepiglottic folds. The primary lesion is classified as follows:

T_1 denotes tumor confined to the laryngeal surface of the epiglottis or one aryepiglottic fold or ventricular band or cavity, mobility not impaired.

T_2 denotes more than one site with normal to slightly impaired mobility.

T_3 denotes tumor which has either fixed the laryngeal structures and/or has invaded the preepiglottic space.

T_4 denotes more extensive than T_3.

Any N category except N_{3A} are included according to the following classification:

N_0 denotes no clinical evidence of cervical lymph node metastasis.

N_1 denotes a single, clinically positive, cervical lymph node 3 cm or less in diameter, not fixed and interpreted as clinically containing metastatic disease.

N_{2A} denotes a single, cervical lymph node, not fixed, more than 3 cm in diameter.

N_{2B} denotes multiple, ipsilateral, cervical lymph nodes that are not fixed.

N_{3A} denotes fixed, ipsilateral, cervical lymph nodes.

N_{3B} denotes bilateral or contralateral, cervical lymph nodes, clinically considered to contain metastasis.

Clinical or radiographic evidence of distant metastasis excludes the patient. Previously treated or inoperable patients are excluded as are those with previous malignant neoplasms except carcinoma of the skin.

The patients are stratified according to sex, T category and N category and are randomized for two treatment options: preoperative radiation therapy and surgery or surgery and postoperative radiation therapy. Dynamic randomization is employed to balance the number of patients in each treatment arm in each institution.

Preoperative radiation therapy consists of 5000 rads from a supervoltage source delivered to the primary and to both sides of the neck in five weeks. The surgery is usually performed four to six weeks following completion of the preoperative radiation therapy but no later than eight weeks after completion of the radiation therapy. Postoperative radiation therapy consists of 6000 rads from a supervoltage source delivered to the primary and 5000 rads to both sides of the neck in five weeks with a 1000 rads boost to residual neoplasm in the neck. The postoperative radiation therapy is initiated as soon as wound healing permits but not later than four weeks following the operation.

TABLE 1. T AND N CATEGORY DISTRIBUTION OF PATIENTS

Category	*No.*	*%*
T_2	14	15
T_3	41	44
T_4	39	41
N_0	44	47
N_1	30	32
N_2	13	14
N_3	7	7
Total	94	

The operation consists of the procedure customarily performed in each institution for that T and N category. The extent of the operation is determined prior to randomization and is not modified according to whether the patient received preoperative or postoperative radiation therapy.

One hundred and ten patients were randomized. Five patients withdrew or were withdrawn. Three patients were found to be ineligible after randomization. Eight patients were entered too recently to have follow-up data available. Therefore, the results in 94 patients have been analyzed. Of the 94 patients, 69 were men and 25 were women. Forty-five patients were less than 60 years of age, and 49 were more than 60 years of age. Of the 94 patients, 14 had T_2 lesions, 41 had T_3 lesions and 39 had T_4 lesions, while 44 were categorized N_0, 30 were categorized N_1, 13 were categorized N_2 and 7 were categorized N (Table 1).

Since patients are still being entered into the study, the results will be presented in blinded fashion. Forty-nine patients were assigned to coded treatment 1 (CT1), and 45 were assigned to coded treatment 2 (CT2). Table 2 indicates the assignment of patients in the various T and N categories to the two treatment options.

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*The following institutions participated in the study: University of Rochester, University of Pennsylvania, Thomas Jefferson University Hospital, Loyola University Medical Center, Ellis Fischel State Cancer Hospital, the Medical University of South Carolina, Columbia Presbyterian Medical Center, Allegheny General Hospital, University of Oklahoma, New York Medical Center, University of New Mexico, Medical Center Hospital of Vermont, University of California at San Francisco, University of Puerto Rico, University of Miami, and University of Virginia.

TABLE 2. CODED TREATMENT (CT) OPTIONS

Category	*CT1*	*CT2*
T_2	6	8
T_3	19	22
T_4	24	15
N_0	24	20
N_1	12	18
N_2	9	4
N_3	4	3
Total	49	45

RESULTS

Death has occurred in 32 or 34% of the patients (Table 3). Nineteen of 49 (39%) of the patients in CT1 and 13 of 45 (29%) of the patients in CT2 have expired. The estimated survival is shown in Table 3. At two years after initiation of therapy, the estimated survival rate is 65%. Based on these early results the difference between CT1 (62%) and CT2 (69%) is not statistically significant.

Sixty-four of the 94 (68%) of the patients show no evidence of disease (NED); 13 of these patients have died free of disease. Table 4 illustrates the distribution of site of first failure for the 30 patients with detectable carcinoma. The carcinoma persisted or became evident first in the primary anatomical site or the cervical lymph nodes in 20 (66%) of the patients. In 7 of those 20 (33%) patients the carcinoma was not completely cleared by the assigned therapy. Failure to clear the carcinoma occurred in the primary site in three patients, in the cervical lymph nodes in two patients and in both the primary site and the cervical lymph nodes in two patients. The first evidence of persistent carcinoma was distant metastasis in nine (30%) of these patients. In one patient the local/regional persistence and distant metastasis were discovered simultaneously.

TABLE 3. ESTIMATED SURVIVAL

	CT1	*CT2*	*Total*
Dead	39%	29%	34%
No. of deaths/ total patients	19/49	13/45	32/94
Months after Randomization			
6	.90	.95	.92
12	.78	.90	.84
18	.70	.81	.75
24	.62	.69	.65

TABLE 4. SITE OF FIRST FAILURE

Total Patients	94
NED	64
Disease Present	30
Site of First Failure	
Local/Regional	20*
Distant Metastasis	9
Both Local/Regional and Distant Metastasis	1

*7 uncontrolled by assigned therapy (3 primary, 2 nodes, 2 both)

The current disease status of the 30 patients in whom carcinoma has been detected following therapy is presented in Table 5. Twelve (40%) of the patients have only local or regional persistence of carcinoma. Eight (27%) of the patients have only distant metastasis, and ten (33%) of the patients have both local or regional persistence and distant metastasis.

TABLE 5. CURRENT DISEASE STATUS

Total Patients	94
NED	64
Disease Present	30
Current Disease Status	
Local/Regional	12
Distant Metastasis	8
Both Local/Regional and Distant Metastasis	10

There has been failure to control the primary lesion in 17 (18%) of the patients (Table 6). Twelve of 49 (24%) of the patients in CT1 and five of 45 (11%) of the patients in CT2 had persistence of the lesion in the primary site. The frequency and duration of the control of the primary is shown in Table 6. At two years after the initiation of therapy, an estimated 80% had no evidence of tumor at the primary site. Based on these early results, the difference between the estimated local

TABLE 6. CONTROL OF PRIMARY LESION

	CT1	CT2	Total
Relapse Rate	24%	11%	18%
No. uncontrolled/ total	12/49	5/45	17/94
Months after Randomization			
6	.96	.93	.95
12	.79	.93	.86
18	.72	.89	.82
24	.72	.83	.80

control rates for CT1 (72%) and CT2 (83%) at two years is not statistically significant.

Thirteen (41%) of the 32 patients who have died were NED. Among the 19 patients who died with disease present, 4 had local or regional carcinoma only, seven had distant metastases only, and eight had both local or regional carcinoma and distant metastases (Table 7).

TABLE 7. DISEASE STATUS AT DEATH

Number of Deaths	32
NED at Death	13
Disease Present at Death	19
Disease Status at Death	
Local/Regional Only	4
Distant Metastasis Only	7
Both Local/Regional and Distant Metastasis	8

The cause of death was a manifestation of the treated primary in six (19%) of the patients, due to distant metastasis in eight (25%) of the patients and attributed to complications of treatment in four (12.5%) of the patients (Table 8). These fatal complications were asphyxia, fistula formation, sickle cell crisis and death during operation.

Fifty-one percent of the patients receiving preoperative irradiation and surgery developed surgical complications, and 22% of the patients treated in this way had severe surgical complications (Table 9). Thirty-nine percent of the patients receiving surgery and postoperative irradiation developed surgical complications, and 7% of the patients treated in this way had severe surgical complications. In the former group, there were 14 with delayed healing, 16 with fistula formation, 3 with carotid artery rupture and 4 with graft failure. The differences in the rate of surgical complications in the two treatment groups was not statistically significant.

TABLE 8. REPORTED CAUSE OF DEATH

Number of Deaths	32
NED at Death	13
Disease Present at Death	19
Cause of Death	
Treated Primary	6
Cervical Nodes	0
Distant Metastasis	8
Treatment Complications	4
Unrelated	11
Unknown	3
Total	32

Forty-seven percent of the patients receiving preoperative irradiation and

TABLE 9. SURGICAL COMPLICATIONS

Type of Complication	Preop Radiation and Surgery	Surgery and Postop Radiation	Total
Delayed Healing	14	9	23
Fistula Formation	16	12	28
Carotid Artery Rupture	3	0	3
Graft Failure	4	1	5
Total %	51%	39%	
% of Severe Complications	22%*	7%**	

*Surgical complication contributed to death in three patients.
**Surgical complication (asphyxia) contributed to death in one patient.

TABLE 10. COMPLICATIONS OF AND REACTIONS TO IRRADIATION

Type of Reaction	*Preop Radiation and Surgery*	*Surgery and Postop Radiation*
Fibrosis	13	14
Necrosis	8	1
Edema	2	4
Lymphedema	1	3
Dysphagia	1	5
Tracheal Stenosis	3	1
Esophageal Stenosis	0	3
Mucositis/Cellulitis/Dermatitis	1	1
Erythema/Desquamation	1	0
Xerostomia	0	1
Infection	0	3
Total %	47%	55%
% of Severe Complications	16%	17%

surgery developed complications of or reactions to irradiation, and 16% of the patients treated in this way had severe complications of irradiation (Table 10). Fifty-five percent of the patients receiving surgery and postoperative irradiation developed complications of or reactions to irradiation, and 17% of the patients treated in this way had severe complications to irradiation. Four patients developed tracheal stenoses, and three patients developed esophageal stenoses. The tracheal stenoses occurred in both treatment groups, but the esophageal stenoses all occurred in the postoperative radiation therapy group. The difference in the frequency of complications of irradiation in the two groups was not statistically significant.

DISCUSSION

Stratification by six T-categories and N-categories within one anatomical site allows meaningful comparison of preoperative radiation therapy and surgery versus surgery and postoperative radiation therapy.

The complication rate of combined radiation therapy and surgery is high but acceptable considering the mortality and morbidity of the natural history of supraglottic carcinoma. The surgical complication rate is not significantly different in the group that received preoperative radiation therapy and the group that received postoperative radiation therapy.

Combined therapy failed to control the carcinoma in 32% of the patients. The site of first failure was in the primary anatomical site or the cervical lymph nodes in 66% of the patients. In one third of these patients, the combined therapy did not result in complete clearance of the carcinoma. Of considerable importance is the fact that the site of first failure was distant metastasis in 30% of the patients. There is no statistically significant difference in the development of distant metastasis in patients who had preoperative or postoperative radiation therapy. Only 40% of the patients dying with detectable carcinoma had only local or regional persistence of carcinoma. Twenty-seven percent had only distant metastasis at the time of death, and 33% had both local or regional persistence of carcinoma and distant metastasis. Forty-one percent of the patients who have died were free of disease at the time of death.

There was failure to control the primary lesion in 18% of the patients. There is no statistically significant difference in the frequency and duration of the control of the primary lesion in the two treatment groups. At two years the rate of control of the primary lesion is estimated to be 80%. However, the survival rate at two years is estimated at only 65%. The difference in survival rates for patients who had preoperative radiation and for patients who had postoperative radiation is not statistically significant.

The discrepancy between a survival rate at two years of only 65% and an estimated primary control rate at two years of 80% can be explained by the presence of distant metastasis only at the time of death in 37% of the patients and by the absence of all disease at the time of death in 41% of those patients who died. There is no statistically significant difference in the disease status at death and cause of death between the two treatment groups.

The high local control and survival rates for supraglottic carcinoma tend to refute the concept that the improvement in survival and local control with combined radiation therapy and surgery has reached a plateau. Since the incidence of distant metastasis in supraglottic carcinoma is high in spite of combined radiation therapy and surgery, improvement in survival and perhaps local control requires employment of some additional modality such as long term cyclical chemotherapy following combined radiation therapy and surgery.

The treatment comparisons presented in this paper are preliminary. Fifty-one (54%) of the 94 patients analyzed are alive and free of disease. Additional accrual and continued follow-up are necessary to determine if the observed treatment differences are important or merely a result of random variation.

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CANADIAN OTOLARYNGOLOGICAL SOCIETY

The annual meeting of the Canadian Otolaryngological Society will be held June 6-8, 1979 at the Harbour Castle Hotel, Toronto, Ontario. Inquiries may be sent to Dr. David Briant, Secretary, St. Michaels Hospital, Toronto, Ontario M5B 1W8.

Ann Otol 87:1978

IMMUNE MONITORING PROTOCOL FOR PATIENTS WITH CARCINOMA OF THE HEAD AND NECK

PRELIMINARY REPORT

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Numerous investigators have observed a depression of cell-mediated immunity in patients with carcinoma of the head and neck using a variety of in vitro and in vivo assays. This report presents the data obtained when a group of head and neck cancer patients were evaluated for reactivity in an in vitro lymphocyte blastogenesis assay using polyclonal mitogens and specific antigens, numbers of peripheral blood T-lymphocytes, and levels of circulating immune complexes. Such an immunological monitoring protocol revealed a depressed reactivity of the cancer patients in the lymphocyte blastogenesis assay when compared to normal age-matched controls. We also observed that 75% of these patients had circulating soluble immune complexes in their sera before and after therapy. These preliminary data indicate that further research is needed to examine the potential role of soluble immune complexes in modulating the host's immune response.

Statistics from the American Cancer Society in 1973 indicate there were 10,650 deaths (8,250 males and 2,400 females) and 15,400 (10,500 males and 4,900 females) new cases of cancer of the head and neck (H and N) including buccal and oropharyngeal sites.

The possible etiology of squamous cell carcinoma of the H and N includes viruses in the Herpesviridiae family,[1-4] host factors as well as environmental factors including pollutants,[5] alcohol[6,7] and tobacco.[8] The role of all of these factors as initiators and/or promotors of the actual carcinogenic event is as yet unclear for H and N cancer. However, their correlation to the malignant process is statistically an irrefutable conclusion.

From the standpoint of the pathogenesis of H and N cancer at least one consistent feature of this disease has been the demonstration of a marked depression of cell-mediated immunity (CMI) in patients prior to and following treatment for their disease. Using in vitro lymphocyte blastogenesis Twomey et al[9] demonstrated a depressed reactivity of H and N cancer patients' lymphocytes to phytohemagglutinin (PHA). Later, also using lymphocyte blastogenesis with polyclonal mitogens, Jenkins et al[10] demonstrated preoperative depression of in vitro blastogenesis but no differences after treatment when compared to properly age-matched controls. A more recent comprehensive study employing numerous in vitro CMI correlates confirmed that a depression in polyclonal mitogenesis exists in all stages of H and N cancer. This was further supported by a consistently decreased mixed lymphocyte culture test.[11] Thymus-dependent lymphocytes (T-cells) have also been shown to be lower than normals for H and N cancer patients.[11,12] Finally, using in vivo contact

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TABLE 1. PATIENT SAMPLE WITH CARCINOMA OF HEAD AND NECK

Pt. No.	*Age*	*Sex*	*Lesion Site*	*Path. Diag.*	*Staging*	*Treat.*
1	73	M	Larynx	S.C.	$T_1N_0M_0$	4500 R
2	60	F	Floor of mouth	S.C.	$T_1N_0M_0$	Surgery
3	53	F	Nose	S.C.	$T_1N_0M_0$	Surgery
4*	57	M	Ear	S.C.	$T_2N_0M_0$	Surgery
5	47	F	Larynx	S.C.	$T_2N_1M_2$	Surgery, 6000 R
6	42	M	Nose	Adenoid cystic ca.	$T_4N_0M_0$	Surgery, 6500 R
7	70	M	Tongue	S.C.	$T_4N_0M_0$	Surgery
8*	58	M	Tonsil/larynx	S.C.	$T_4N_0M_0$	7500 R
9	62	M	Larynx	S.C.	$T_4N_0M_0$	Expired
10	43	M	Larynx	S.C.	$T_4N_2M_0$	Surgery, 3560 R
11	71	M	Parotid	Adenoca.	None	Surgery, 5000 R

*Patients known to have expired at the time of preparation of this manuscript. S.C. - Squamous cell; R. - Rads.

skin sensitization with DNCB and a subsequent 48-hour challenge delayed cutaneous skin test Maisel and Ogura,[13] and Hilal et al[14] observed a depressed CMI reactivity of H and N cancer patients pre- and postoperatively.

Another parameter that may be relevant to understanding the pathogenesis of H and N cancer as well as other neoplastic diseases of man or animals involves the presence of immune complexes in the sera of hosts with such disorders.[15-19] These immune complexes are found either in the peripheral circulation or they may exist as (viral-antiviral-complement [C]) deposits in renal glomeruli of animals with a variety of viral-induced malignancies.[20] There are occasional reports of IgC deposits in glomeruli of humans with leukemia, lymphoma and Hodgkin's disease,[21] Burkitt's lymphoma[22] and several other malignancies.[23-25] In a few of the above studies evidence also suggests that the complexes may contain tumor associated antigens. The role of such factors in the immunopathology of cancer becomes a most important facet of understanding the pathogenesis of both human and animal malignancies.[17,19,26]

The recent availability of a sensitive reproducible radioimmunoassay (RIA) for soluble immune complexes (IC)[16] and its application to a variety of neoplastic diseases[27] provides a rational basis for its inclusion in an immune monitoring protocol. The decision to use the assay was made possible through preliminary data we obtained on an H and N cancer patient sample indicating a 75% incidence of IC in their sera.[25] Hence, one of our objectives was to evaluate the reactivity of H and N cancer patients' lymphocytes to polyclonal mitogens and specific recall antigens in vitro, and to couple these data to a search for circulating soluble IC in these patients' sera. Secondly, through this data, we hope to achieve a better understanding of the pathogenesis of H and N cancer, as we also hope to develop a protocol that would be of value to clinicians in assessing patient prognosis.

MATERIALS AND METHODS

Patient Sample. Eleven patients with cancer of the H and N were selected for the study. The age range was 42-73 years with a mean of 57.8 years and included nine males and two females. Additional data including TMN staging is summarized in Table 1.

Ten noncancer surgerized controls were selected by the ENT staff and matched according to the amount of surgical trauma and anesthesia compared to their cancer counterparts. Also, ten normal controls, age and sex matched, were selected from faculty and staff of the WVU Medical Center. The cancer and noncancer surgery controls were sampled at pretreatment and at monthly intervals. Normal controls were also sampled at monthly intervals.

Blood Sample Processing. At each patient visit 10 ml of clotted blood serum and 20 ml heparinized blood was obtained. The serum was harvested, aliquoted and stored at −80 C. The heparinized blood was layered onto precooled Ficoll-Paque* gradients and centrifuged at 400 xg for 30 minutes. The plasma layer was harvested and divided into two aliquots. One aliquot was used as a source of autologous plasma in the microlymphocyte blastogenesis assay. The other plasma sample was frozen at −80 C to be assayed for soluble immune complexes.

The lymphocyte layer that had formed at the gradient interface was harvested, washed twice in .01M phosphate buffered saline, pH 7.2, (PBS) and the cell concentration was adjusted to 1 x 10^7 cells/ml. This lymphocyte suspension was used for all cell-mediated assays.

ASSAYS FOR CELL-MEDIATED IMMUNITY

T-Cell Quantitation. The active sheep erythrocyte rosette test was used.[14] Approximately 10^6 lymphocytes were mixed with 0.2 ml of sheep erythrocytes adjusted to 4 x 10^7 cells/ml. This mixture was incubated at 37 C for 15 minutes, pelleted at 400 xg for 5 minutes and incubated another hour at 4 C. The cell pellet was gently resuspended and the percent of lymphocytes which bound 3 or more SRBC forming rosettes were counted using a hemacytometer.

Microlymphocyte Blastogenesis Assay. Sterile, plastic microtiter U-plates** were used for the assay. One plate was used to assess the response of lymphocytes to polyclonal mitogens, phytohemagglutinin (PHA)† and concanavalin-A (Con-A)†† and a separate plate was used to assess the response of lymphocytes to specific recall antigens.

Ten wells per plate were used as replicate controls and contained 0.1 ml of RPMI-1640 without serum. The specific recall antigens and polyclonal mitogens were prepared in RPMI-1640 with serum and were added to four replicate wells in 0.1 ml volumes. The concentration of these reagents which gives optimal lymphocyte stimulation had been predetermined experimentally using normal donors. For the polyclonal mitogens, each of the four replicate wells received 2μg of PHA and Con-A in 0.1 ml of RPMI-1640.

For the specific recall antigens, the test dilutions were: tetanus toxid (1/320), streptokinase-streptodornase (SK-SD) (1/640), and influenza A-2 virus vaccine (1/80). Again each specific recall antigen was added to each of four replicate wells in a volume of 0.1 ml of RPMI-1640. All wells in both plates then received 0.1 ml of the lymphocyte suspension diluted to contain 5 x 10^5 cells in RPMI-1640 supplemented with 40% autologous patient's plasma, yielding a final serum concentration of 20%.

On day three of the incubation period each well of the polyclonal mitogen plates received 0.01μCi of ^{14}C-thymidine per well. Similarly, on day five isotope was added to the specific recall antigen plates. Eighteen hours later the lymphocytes were harvested onto filter paper strips with a semi-automated cell harvestor.‡ The cells were dried overnight, the scintillation cocktail (toluene = 1 liter, PPO = 5.0g, POPOP = 0.1g), added and the vials counted.‡‡

Data were always expressed as lymphocyte stimulation indexes calculated by dividing the mean cpm of the stimulated lymphocytes by the mean cpm of the control unstimulated lymphocytes.

Detection of Immune Complexes. A radioimmunoassay (RIA)[18] which employs the B-lymphoblastoid Raji cell line was used to quantitate immune complexes in patients' sera.

Statistical Methods. We employed a nonparametric statistical test to analyze our data because of the nonnormal distribution resulting from biological variation of the lymphocyte stimulation assays. The Wilcoxon rank-sum test[20] was used to compare the pretherapy and posttherapy group of cancer patients to each other and to the above designated controls. The null hypothesis stated that no data pair was significantly different. The alternate hypothesis stated a data pair was different and indicated the direction of that difference.

RESULTS

In Table 2 we summarize the pretherapy status of our patient sample with respect to all parameters measured. Also included are the means for the cancer patients (group A) and their normal counterparts (group D). The range of values for IC was 0-54 μg eq/ml with a mean of 25.5 These values were significantly elevated over normals of group D and noncancer surgerized controls of group C (Table 4). Also, Table 4 illustrates that the PHA stimulation indexes of the controls were significantly less than the pretherapy cancer patients. This may be the result of two very high PHA stimulation indexes and also due to our small patient sample. Regarding the specific recall antigen data, Table 4 reveals that SK-SD and

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*Pharmacia Fine Chemicals Inc., Piscataway, NJ.

**Nunclon Delta, Denmark.

†Difco, Detroit, MI.

††Miles Laboratories, Elkhart, IN.

‡Model M-12 cell harvester, Brandel Instruments, Bethesda, MD.

‡‡Model 3320 LS Counter, Beckman Instruments, Fullerton, CA.

TABLE 2. PRETHERAPY IMMUNE STATUS OF HEAD AND NECK CANCER PATIENTS

	*Immune Complexes**	*Lymphocyte Blastogenesis Assays***					*T-Cells (%)*†
Pt. No.	*µg AHG eq/ml*	*PHA*	*Con-A*	*SK-SD*	*Tet.*	*Inf.*	*E-Rosettes*
1	25	22.70	17.30	0.85	0.83	0.83	18
2	68	102.00	75.50	2.30	2.70	4.25	27
3	0	27.80	57.40	1.15	0.98	4.67	37
4	30	24.40	40.00	5.96	3.89	2.57	23
5	15	21.60	22.50	4.69	1.04	1.77	23
6	27	44.40	27.60	5.30	1.29	3.44	21
7	0	69.20	38.50	1.22	0.86	0.93	15
8	0	53.60	27.90	2.50	1.10	3.10	25
9	54	5.20	0.50	1.70	0.90	0.90	26
10	36	117.00	16.00	3.59	1.23	5.52	8
x̄ cancer†† (group A)	25.50	48.79	32.32	2.93	1.48	2.79	22.3
x̄ normals (group D)	1.9	35.30	46.68	4.80	1.92	2.51	23.4

PHA - Phytohemagglutinin. Con-A - Conconavallin-A. SK-SD - Streptokinase-streptodornase. Tet - Tetanus toxoid. Inf - Influenza A-2 virus vaccine.

*Radioimmunoassay as performed by the method Theofilopoulos.[16]

**The data is expressed as a ratio of the cpm of the controls divided by the cpm of stimulated lymphocytes.

†The active rosette test as performed by the method of Wybran.[29]

††Statistical analysis employed the Wilcoxon test[30] and the results are summarized in Table 4.

tetanus toxoid stimulation indexes of pretherapy cancer patients were significantly depressed over normals. All other parameters tested were equivalent by the Wilcoxon test.[30]

Table 3 provides data for our cancer patients at the first posttherapy visit (group B) and also provides the means for the matched normals and the noncancer surgerized controls (group C). A statistical analysis of this data, as seen in Table 4 revealed that only the IC were significantly elevated over controls. Of interest is the observation that noncancer surgerized controls had significantly depressed stimulation indexes for PHA and Con-A but not specific recall antigens when compared to age-matched normals. Also, the T-cell counts were significantly depressed in the post-surgery noncancer control group (Table 4).

Finally, analysis of the pretherapy (group A) versus posttherapy (group B) status of assayed parameters is also reviewed in Table 4. The data showed the SK-SD stimulation index and T-cell count to be depressed at posttherapy but all other parameters were equivalent except for IC. The latter were significantly increased from pretherapy to the first posttherapy visit.

The merits of the experimental protocol became more apparent when it was applied to longitudinal monitoring. Figure 1 illustrates the findings for Patient 1 who was followed from February 29, 1977 to August 24, 1977. A most interesting observation was the dramatic and persistent increase in circulating soluble IC posttherapy and the concomitant decline in polyclonal mitogen reactivity. Also noted was a consistent depression of specific recall antigen reactivity.

Figure 2 displays the data of Patient 2 who likewise showed an increase in levels of soluble IC in his sera posttherapy, accompanied with a decline in polyclonal mitogen reactivity. However, specific recall antigen reactivity was normal throughout the period of patient sampling.

The data on Patient 11 is shown in Figure 3. Subsequent to surgery and postoperative irradiation, he demonstrated a marked increase in IC levels on June 23, 1977. The latter correlated

TABLE 3. POSTTHERAPY IMMUNE STATUS OF HEAD AND NECK CANCER PATIENTS

	*Immune Complexes**	*Lymphocyte Blastogenesis Assays***					*T-Cells (%)†*
Pt. No.	*μg AHG eq/ml*	*PHA*	*Con-A*	*SK-SD*	*Tet.*	*Inf.*	*E-Rosettes*
1	66	118.00	26.00	2.10	1.50	0.85	10
2	62	110.00	86.00	12.90	4.60	5.10	21
3	0	29.50	26.80	1.49	1.52	3.60	22
4	60	9.80	29.00	2.40	1.54	1.22	30
5	45	21.50	22.40	4.69	0.80	1.77	23
6	18	6.60	11.90	1.87	1.25	1.26	20
7	0	10.00	8.20	8.90	1.19	1.20	27
8	16	3.70	10.70	1.00	1.00	4.60	18
9	Expired						
10	30	21.00	35.00	1.60	1.30	1.80	28
x̄ cancer†† (group B)	33	36.60	28.40	4.09	1.63	2.30	22.10
x̄ normals (group D)	1.90	35.30	46.68	4.80	1.92	2.51	23.40
x̄ surgery (group C)	1.36	21.39	26.40	3.10	1.75	1.97	21.36

See Table 2 for explanation of abbreviations.

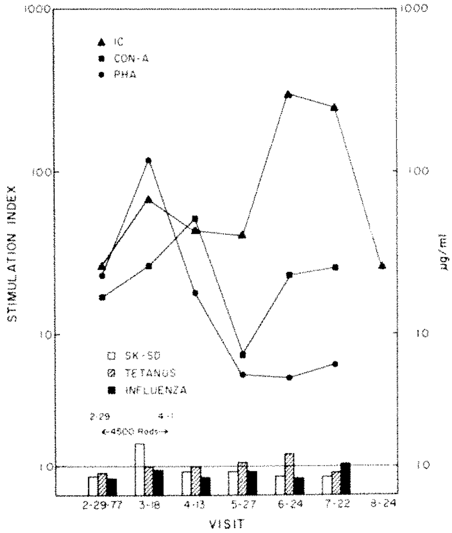

Fig. 1. Immune monitoring of Patient 1. A 73-year-old male Caucasian diagnosed with $T_1N_0M_0$ squamous carcinoma of the larynx. Treated with total of 4500 rads in 25 doses for five weeks. Left x-axis displays the stimulation indexes for all mitogens and lymphocyte blastogenesis. Right x-axis illustrates in μg AHG, eq/ml of serum the concentration of soluble immune complexes. All data was plotted on 3-cycle semilogrithmic graph paper.

with a depression in polyclonal mitogen reactivity but an unaltered normal response to specific recall antigens.

DISCUSSION

An experimental immune monitoring protocol combining the quantitation of circulatory soluble IC with the assay of in vitro CMI parameters was evaluated on a small group of H and N cancer patients and matched controls. The protocol proved to be most valuable for assessing changes in immunological parameters when it was applied over several patient visits.

The quantitation of IC revealed this parameter to be significantly increased at the first visit in the H and N cancer patients. A further increase at the first posttherapy visit was noted. Increased levels of IC in patients' sera persisted for several months in the three patients monitored longitudinally. The measurement of soluble IC in cancer patients[27] has revealed that in certain types of malignancies such as melanoma, carcinoma of the colon and breast, and osteogenic sarcoma, the patients have a high incidence of IC in their sera. However, such surveys have not included patients with carcinoma of the H and N. Recently, in a preliminary report, we dem-

TABLE 4. STATISTICAL ANALYSIS OF ALL DATA IN TABLES 2 AND 3 BY THE WILCOXON TEST

Data Pairs	*IC*	*PHA*	*Con-A*	*SK-SD*	*Tet.*	*Inf.*	*T-Cells*
D x A	D<A	D<A	0	D>A	D>A	0	0
D x B	D<B	0	0	0	0	0	0
A x B	A<B	0	0	A<B	0	0	A<B
D x C	0	D>C	D>C	0	0	0	D>C

Groups: A - Pre-therapy cancer. B - Post-therapy cancer. C - Normal-Surgerized Controls. D - Normal Controls. Hypotheses: H_0 - The data pairs are equivalent. H_1 - The data pairs are not equivalent. Results: 0 - No significant difference at alpha = 0.05. > - Significantly greater than. < - Significantly less than.

onstrated 75% of patients with carcinoma of the H and N to possess soluble IC in their sera[28] employing the fluorescent antibody Raji cell test.[31] This manuscript reports that 8 of 11 H and N cancer patients (73%) had sufficient IC for quantitation, when the RIA method of Theofilopoulos et al[16] was utilized. A high incidence of soluble IC as we observed in H and N cancer patients, has been reported for other malignancies[27] and in disorders with an infectious component.[16,32] Furthermore, attempts have been partially successful in identifying the antigenic component bound to IgG of the IC which adheres to the C receptor of the Raji cell. In Burkitt's lymphoma, an Epstein-Barr virus coded antigen was identified[22] and for colon carcinoma CEA was found and a tumor associated antigen (TAA) was found for melanoma and osteogenic carcinoma as well.[27] Relevant to these observations is the data supporting the production of complement-fixing (CF) antibodies to

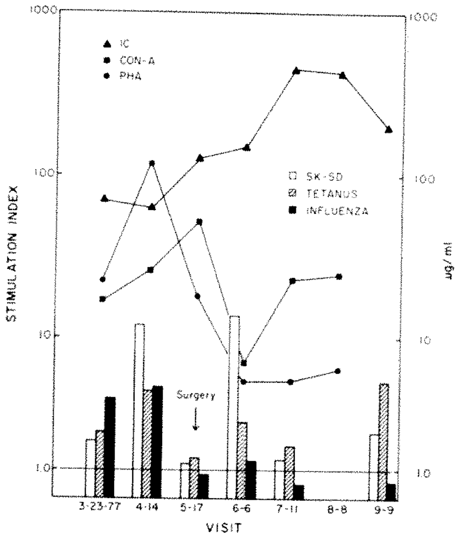

Fig. 2. Immune monitoring of Patient 2. A 60-year-old female Caucasian diagnosed with $T_1N_0M_0$ squamous carcinoma of the floor of the mouth treated by right modified neck dissection on 5-17-77. All data is expressed as in Fig. 1. Patient was doing well at the time of preparation of this manuscript.

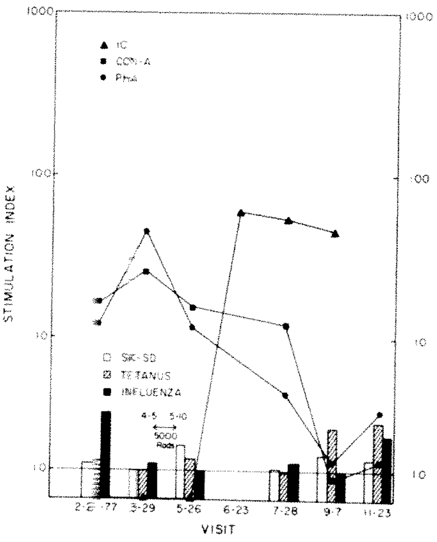

Fig. [illegible]. Immune monitoring of Patient 11. A 7[illegible]-year-old male Negro diagnosed with an adenocarcinoma of the right parotid. Total parotidectomy, right radical neck dissection was performed on 3-3-77. Postsurgery radiation therapy involved 5000 rads in 25 doses from 4-5-77 to 5-10-77. Rhytidoplasty was performed on 9-8-77 without complications. All data is expressed as in Fig. 1. Patient was doing well at the time of preparation of this manuscript.

herpes simplex virus — non-virion antigens (HSV-NVA)[1-3,33] by patients with carcinoma of the H and N. Also, such CF antibodies have been shown to persist following successful treatment of the H and N cancer, especially laryngeal carcinoma.[3] A reasonable approach now would be to conduct similar experiments with H and N cancer sera centering efforts on identification of possible HSV-NVA.

The analysis of in vitro lymphocyte stimulation and T-cell data at pretherapy and posttherapy revealed some statistically significant differences when compared to matched normals. The pretherapy response of cancer patients' lymphocytes indicated depressed stimulation indexes for SK-SD and tetanus but polyclonal mitogen reactivity was not different, probably due to artifacts introduced by selected patients with elevated stimulation indexes and to the small patient sample. Such altered reactivity of H and N cancer patients in the lymphocyte stimulation assays is supported by the literature but primarily with polyclonal mitogens.[9-11] However, a recent report suggests these assays have significant variability and no single test system is adequate.[11]

At the first posttherapy visit the significant depression of SK-SD lymphocyte reactivity persisted and the percentage of T-cells tested by the E-rosette method were decreased at this visit. All other test parameters at the first postoperative visit were not different when analyzed by the same Wilcoxon procedure.[30] We also observed a depression of in vitro blastogenesis for PHA and Con-A and T-cell counts for normal-surgerized controls when compared to normals. The latter supports findings by Slade et al[34] and indicates that surgery alone may explain in part the altered CMI reactivity noted at the first posttherapy visit for the H and N cancer patients who undergo surgery. The data indicate that no single immune parameter is adequate to assess any patient's response to his tumor and that age-matched controls are a necessity.[11]

Many of the above designated problems were overcome when the protocol was applied to the longitudinal monitoring of the three H and N cancer patients included in our study. The value of quantitating soluble IC became even more apparent, especially when considered in conjunction with the several immune parameters included in the protocol. For example, we observed a correlation between increasing levels of circulating soluble IC with the depression of either polyclonal mitogen and/or specific recall antigen blastogenesis, and interpretation of such findings is relevant to the pathogenesis of H and N cancer. One must consider the possible effects of immune complexes on the malignant process. Such IC may effect the immune response to the tumor by masking TAA,[18] including antibody-dependent cellular cytotoxicity,[35] blockage of lymphocyte reactivity as a result of antigen excess,[36] lysis of T-lymphocytes via Fc receptors and C,[37] or by altering the lymphoproliferative response of lymphocytes to antigens.[38-40] The approach to evaluating these possible mechanisms necessitates isolation and purification of the IC[27] or other factors which might modify the CMI response,[41-43] and directly assess their role in blocking various in vitro CMI assays.

In summary, we have demonstrated that the use of multiple immune parameters are of value in assessing the CMI status of H and N cancer patients during treatment. Also, the most consistent parameter detected pre- or postherapy was the presence of significant levels of soluble IC in their sera. A correlation between elevated levels of soluble IC and depressed lymphocyte reactivity to mitogens during monitoring of three patients was noted.

These preliminary data indicate that there are certain defects in T-cell related functions in H and N cancer patients which were related to the presence of elevated levels of immune complex-like substances. It is important to expand such studies to a larger patient sample in order to assess the value of our research to understanding the pathogenesis of H and N cancer.

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INTERNATIONAL CONGRESS ON EDUCATION OF THE DEAF

The International Congress on Education of the Deaf will be held in Hamburg, West Germany, August 4-8, 1980. For further information write: German Convention Service, Hamburg Office, Hohe Bleichen 13, D-2000 Hamburg 36.

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THOROTRAST® INDUCED PHARYNGEAL NECROSIS

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Thorotrast®, a radioactive contrast material used between 1930 and 1950, is often permanently retained within the patient. Individuals who have had diagnostic studies with Thorotrast® may develop serious complications many years later. These complications fall into two major categories, desmoplastic and neoplastic. The inadvertent infiltration of Thorotrast® into soft tissue, usually the neck during carotid arteriography, may later result in severe fibrosis with constriction of the surrounding vessels and nerves. Malignancies, the second major problem, have occurred at the site of previous Thorotrast® instillations throughout the body. The following report describes the clinical course of an 82-year-old woman who presented with a Thorotrast® induced desmoplastic reaction of her neck, complicated by pharyngeal necrosis and the development of a pharyngeal cutaneous fistula. The latter problem is quite rare, having been previously reported only once. Despite extensive tissue destruction conservative management prevailed. Repetitive debridement, controlling the intermittent infections, maintaining her nutritional status, and relieving her pain allowed spontaneous healing to occur.

Thorotrast® is the proprietary name of a radiographic contrast medium composed of a colloidal suspension of ^{232}thorium dioxide in a dextran medium. During the 20 years following its introduction in 1930, it has been estimated that as many as 100,000 people have been subjected to various radiographic studies utilizing Thorotrast®.[1]

Thorotrast® is an effective, extremely visible contrast substance due to the high density of its atom. It was widely used in intravascular studies (primarily carotid angiography) because of its high visibility, and in the event of perivascular infiltration, its inertness made it relatively painless with a low incidence of vascular spasm. When Thorotrast® is injected into the general circulation, it is removed and stored by the fixed phagocytes of the reticuloendothelial system, hence the dye is concentrated in the liver, spleen, lymph nodes, and bone marrow. This property made it a valuable tool in radiographic studies of these organs.

However, ^{232}thorium dioxide is a radioactive substance, emitting during its decay series alpha (90%), beta (9%), and gamma (1%) radiation. The physical half-life of ^{232}thorium dioxide and its primary daughter products (mesothorium, radiothorium and thorium X) is no less than 13.9 thousand million years (1.39×10^{10}).

Since the excretion of ^{232}thorium dioxide and its daughter products is negligible, the body becomes the permanent repository of these radioactive substances. This prompted the Council of Pharmacy and Chemistry of the American Medical Association in 1932 to condemn its use.[2] Even though investigators in the 1930s demonstrated its carcinogenic potential in the experimental animal,[3,4] the substance was widely used in most countries of the world until the early 1950s. (France, however, banned the use of Thorotrast® in 1935.)

MacMahon,[5] in 1947, reported the first fatality due to a Thorotrast® induced endothelial cell sarcoma of the liver. This was rapidly followed by numerous other reports of thorium induced malignancies throughout the

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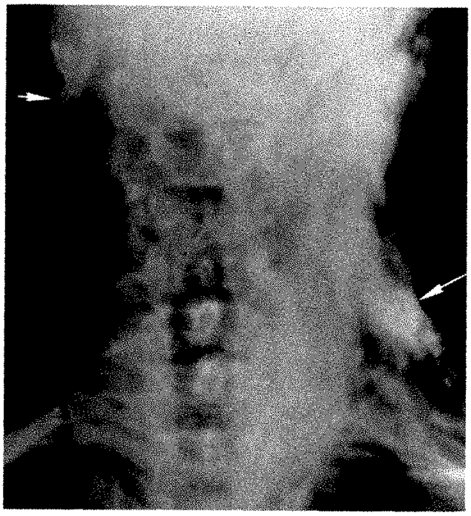

Fig. 1. Soft tissue views of the neck show calcifications along both carotid arterial systems, but chiefly on the left (arrows).

body, and the use of Thorotrast® fell into disfavor.

The following patient illustrates two delayed complications which may occur following the inadvertent perivascular infiltration of Thorotrast®. The first, a thorotrastoma (severe desmoplastic reaction) is relatively common, the second problem, pharyngeal necrosis, is quite rare, having previously been reported in only six patients.[6-9] Pharyngeal cutaneous fistula formation secondary to pharyngeal necrosis has been reported only on one other occasion.[9]

CASE REPORT

The patient, an 82-year-old woman, developed cervical pain and difficulty in swallowing in August 1972. However, she was not seen in our clinic until two months later. At this time her discomfort was so severe that she was able to swallow only liquids.

Her past medical history was significant because in 1951 a carotid arteriogram was done in Detroit, Michigan to evaluate a "seepage of the brain." The patient, despite repeated questioning, was unable to relate more details regarding this test, and could not even remember the name of the hospital where the study had been performed.

The initial physical examination revealed a large ulceration in the patient's right oral pharynx which extended above the soft palate. Bilateral woody induration of her neck was present, worse on the left. A left vocal cord paralysis was present. The remainder of her physical examination was within normal limits.

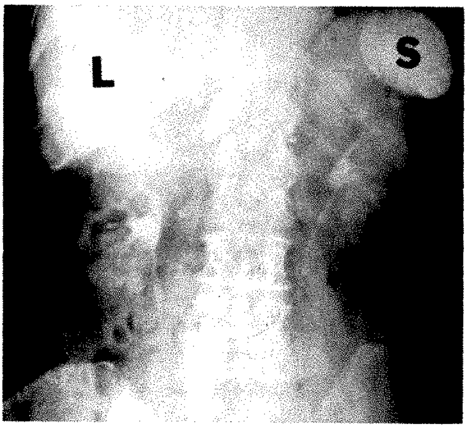

Fig. 2. Radiographic flat plate of abdomen reveals radiopaque material in liver (L) and spleen (S). (A recent intravenous pyelogram accounts for the dye within the renal collecting system.)

The routine laboratory studies were normal. Radiographic examination of the skull revealed a calcified lesion in the suprasellar area, probably representing a craniopharyngioma. Soft tissue views of her neck showed calcifications along both carotid arteries, more severe on the left (Fig. 1). A radiographic flat plate of her abdomen showed radiopaque material in the liver, spleen, and periaortic nodes (Fig. 2).

A biopsy taken from the oral lesion revealed hyperkeratosis of the epithelium with underlying fibrosis, chronic inflammation, and areas of necrosis. A brown granular substance was seen scattered through the subcutaneous tissue (Fig. 3).

Because the histological and clinical findings were consistent with a thorotrastoma, an autoradiograph of the biopsy specimen was done to determine the presence of radioactivity. A slide of the lesion was immersed in Eastman Kodak NTB emulsion, which had been melted at 40 C. The preparation was allowed to dry in a vertical position at 25 C and a 75% relative humidity. The slides were stored in a light-tight box, in a dry oxygen free atmosphere at 4 C for one week. The slides were developed in Eastman Kodak D 72 for three minutes. This procedure demonstrated the classic "tracks" of alpha radiation.

The diagnosis of thorium granuloma of the neck with secondary necrosis of the oro- and nasopharynx was made. An examination under general anesthesia revealed the ulcer extended to the base of the patient's skull.

A neurosurgical consultant recommended no therapy for the craniopharyngioma. The patient was treated symptomatically with naso-

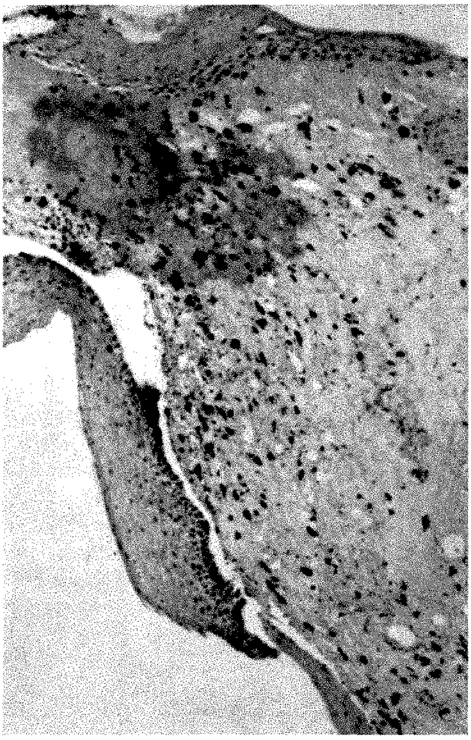

Fig. 3. Biopsy near the nasopharyngeal ulcer reveals acute and chronic inflammation; note granular substance (Thorotrast®) scattered throughout subcutaneous tissue. (H & E)

gastric feedings and Xylocaine® Viscous for pain. At this time, because of the location of the ulceration, we were concerned that spontaneous rupture of the carotid artery was a likely possibility, yet the extent of the lesion to the base of her skull precluded any definitive treatment.

One month later the oro- and nasopharyngeal lesion on the right began to improve; the necrotic area sloughed, the base became clean and showed signs of healing. However, at this time she developed a large ulcer in her left pyriform sinus also involving the esophageal inlet. A direct laryngoscopy and biopsy were done. The histological examination again showed thorium granuloma. The tissue destruction in this area was extensive enough so that pieces of necrotic prevertebral fascia were removed with the biopsy and debridement.

The patient was again treated conservatively with analgesics while her nutrition was maintained with nasogastric feedings. A barium study at this time illustrated both the nasopharyngeal ulcer and the closing of the esophageal inlet secondary to the surrounding tissue edema (Fig. 4).

The patient, over the next two months, developed intermittent pain and swelling in her left neck, which finally broke down into a spontaneous pharyngealcutaneous fistula. Cultures from this area grew out *Hemophilus influenza*. The patient was treated with ampicillin with resolution of the superficial infection.

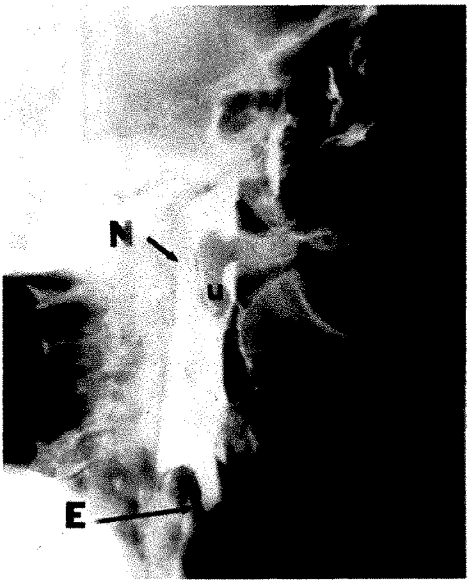

Fig. 4. Barium esophagram illustrates total esophageal obstruction secondary to edema around the esophageal inlet (E). Note that no barium passes beyond this point. Pharyngeal ulceration can also be seen. "N" points to upper edge of ulceration. Note this extends well above the uvula (U).

Surprisingly, over the next several months the patient began to gradually recover. By May 1973, the patient's nasopharyngeal lesion had healed completely. Although a depression still remained in the area, it was lined with mucosa. Palatal closure was sufficient enough so that nasal regurgitation was not a problem. The pyriform sinus and esophageal inlet lesions also gradually healed spontaneously although laryngeal edema was present for several additional months.

She continued to improve and, by August 1973, one year following her original complaints, the patient was symptom free. Her physical examination at this time was within normal limits with the exception of persistent left vocal cord paralysis and woody induration of her neck. The mucosal lined oro- and nasopharyngeal defect has remained (Fig. 5), however, the patient's palatal closure is adequate and she has no difficulty in eating.

Over the intervening five years the patient has continued to do well, and has developed no new problems.

DISCUSSION

The vast reservoir of patients who

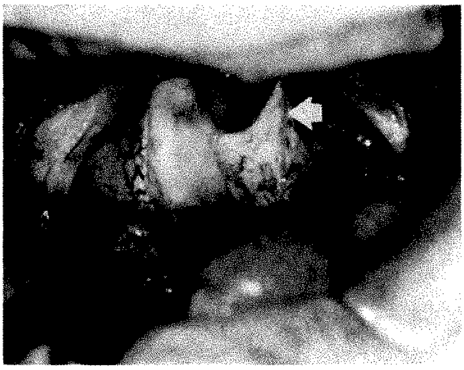

Fig. 5. Five years later the pharyngeal defect remains. It is completely healed, however, and mucosa-lined. Arrow points to left lateral border of ulceration. Note that it extends above the uvula. Posterior tonsillar pillars are also well seen.

have had radiographic studies with Thorotrast® all have the potential to develop either cancer or severe desmoplastic reactions.

Diagnosis. Since the diagnostic study utilizing Thorotrast® may have preceded the development of a complication by several decades, it is not uncommon for the patient to have either forgotten or overlooked the contrast study in their history. The diagnosis, in these instances, may be made by a combination of radiographic evaluation, histological studies, and measurement of the residual radioactivity from the biopsy specimen.

When Thorotrast® has been utilized to outline hollow body cavities, the retained dye may be seen on routine radiographic studies of these organs. If the previous contrast study was by the intra-arterial route, the Thorotrast® is then concentrated in the liver, spleen, periaortic nodes, and bone marrow. In these instances, an abnormal flat plate radiograph will often show an outline of these organs due to the retained dye. In the event of accidental perivascular injection of Thorotrast®, later soft tissue radiographs will show a marked increase in the density of the tissues surrounding the vessels. This is due to the particulate Thorotrast® itself, and to calcifications which occur in the dense scar tissue.

The histologic changes that occur when Thorotrast® is introduced into the soft tissues of the body (usually the neck following accidental perivascular infiltration), consist of an early acute inflammatory reaction which later resolves. Later there is a deposition of fibrous tissue and calcifications. Macrophages, giant cells, and lymphocytes are commonly seen surrounding the brown highly refractive foreign body granules which represent the Thorotrast®. The Thorotrast® granules are not always surrounded by this cellular infiltrate, but also may appear free within relatively normal appearing tissue.

The measurement of residual radioactivity of thorium deposits is an important adjunct in the diagnostic evaluation. Scintillation scanning over the involved area may reveal increased gamma radiation, however, the principle type of radioactivity from thorium and its daughter products, alpha radiation, will not be measurable by this method because of its low tissue penetrance. However, tissue from a biopsy specimen evaluated with the scintillation scanner will reveal the characteristic radioactive spectrum. A simple method to determine the presence of radioactivity is to place a biopsy specimen on an undeveloped radiographic film for 48 hours in a dark room. If radiation is present, an area of development will occur, appearing as a white spot on the radiographic film. Of course, the more refined technique of autoradiography previously described in the case report will demonstrate the actual "tracks" made by the individual alpha particles.

Complications. The carcinogenic potential of radioactive thorium dioxide was suspected in the 1930s when several studies produced neoplasm in the experimental animal.[3,4] Since MacMahon[5] reported the first Thorotrast® induced human liver sarcoma in 1947 the literature has become replete with additional reports. Malignancies due to Thorotrast® may be divided into three categories: 1) Those that appear at the site of a previous injection. These would include the sarcomas that have occurred in patients who have had the accidental perivascular injection of Thorotrast® into their necks; 2) Tumors secondary to retained Thorotrast® deposited in hollow body cavities. These include cancer of the breast after mammography,[10] cancer of the kidney after pyelography, cancer of the bronchus after bronchography, and cancer of the eyelid after dacryocystography.[11] Of particular interest to the otolaryngologist is the development of cancer of the maxillary sinus following the intraluminal installation of Thorotrast®;[12-14] 3) Malignancies of the reticuloendothelial system which are relatively common since systemically injected Thorotrast® is retained by these cells. The greatest number of Thorotrast® induced malignancies are of the liver.[11]

As with any intravascular administration through the percutaneous route, inadvertent local infiltration may occur. The accidental deposition of Thorotrast® into the soft tissues of the neck in one series,[7] was seen in 3% of the patients undergoing carotid arteriography. When this occurs, at least half of the patients will later develop a reaction to the dye consisting of a severe desmoplastic reaction known as a thorotrastoma.

A cervical thorotrastoma usually begins as a firm, gradually enlarging neck mass. The increase in size is due to the migration of the macrophages which have ingested the particles of the dye, and to the natural downward gravitational pull along the facial planes of the neck. It is not uncommon for these lesions in their latter stages to extend from the base of the skull to the upper mediastinum.

As the enlarging lesion surrounds the adjacent nerves, blood vessels, and muscles the intense fibroplastic activity interferes with their function. The patient then may develop a weakness in the glossopharyngeal, vagus, spinal accessory, or hypoglossal nerves and sympathetic trunk. The severe fibrosis may also cause gradual obliteration of the carotid and subclavian arteries.[9,15] The desmoplastic reaction itself often encases the muscles of the neck, resulting in their decreased mobility.

Development of pharyngeal necrosis is a rare complication seen in patients with thorotrastomas, having been previously reported only six times.[6-9] The necrosis is thought to be due to the cicatricial reaction interfering with the local blood supply rather than secondary to radionecrosis of the tissue.[9,15]

The management of thorotrastomas is still controversial. One school of thought is to simply follow these patients and treat the complications as they arise.[16-19] Hoarseness due to recurrent laryngeal nerve involvement is a common complaint seen in patients with thorotrastomas and has been corrected with Teflon® injection.[17-20] Other clinicians take a more aggressive attitude toward thorotrastomas and indicate radical neck dissection as the treatment of choice.[9,20,21] They reason that the lesion is one of gradual enlargement and removal should be done before the patients develop symptoms of neural or vascular compression. The possibility of a malignancy arising in a thorotrastoma, although remote, is still there. Although complete removal of the Thorotrast® is usually impossible due to the wide dispersion in the facial planes of the neck, removing the bulk of the substance will significantly reduce the total area under radioactive exposure.

In the patient we have described, aggressive surgical intervention was not possible for two reasons: 1) the ulcerative lesion on the right extended to the base of her skull far beyond the limits of resectability; and 2) the presence of bilateral thorotrastomas created a great possibility of compromise in both carotid arterial systems.

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TREATMENT OF RADIATION-INDUCED TISSUE INJURY BY HYPERBARIC OXYGEN

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Hyperbaric oxygen therapy appears to be a beneficial adjunctive treatment modality in the management of radionecrosis of bone and soft tissue in the head and neck. The mechanism of such wound healing enhancement appears to be related to oxygen stimulation of fibroblastic activity and neovasculation. In this pilot study, involving 13 cases of refractory mandibular radionecrosis treated with hyperbaric oxygen, complete healing of soft tissue disease with covering of exposed bone has been noted in seven cases 11 to 27 months posttreatment; transient healing was seen in three cases; moderate to marked improvement in soft tissue disease has been noted in three cases. Pain relief was marked in six cases, moderate in four cases, and slight in one case of the 11 patients with significant pretreatment pain. Radiographic improvement was slight to moderate in ten cases. Four of the five patients with pathologic fractures developed a firm fibrous union of the mandibular segments during or shortly after treatment. Three additional cases of head and neck radionecrosis of other sites have noted significant improvement in their lesions during treatment. Three other patients with radionecrosis of the foot, hip, and vagina have also been treated with good results only in the vaginal case. None of the 19 patients treated with hyperbaric oxygen developed persistent or significant complications.

Tumoricidal doses of radiation frequently produce irreversible damage to healthy tissues adjacent to the tumor site. Since the advent of supervoltage therapy and refined dosimetric techniques, these complications have become less common, but are still seen. The pathology of such damage is characterized by a progressive, obliterative endarteritis with a subsequent decrease in blood flow to the tissues supplied by these vessels. Necrosis with tissue breakdown and secondary infection then occurs and enhances the effects of the obliterative endarteritis. In patients who undergo head and neck cancer surgery after radiation therapy, ischemic surgical wounds with secondary infection and impaired healing are frequently seen. In nonoperated patients, radionecrosis of bone and soft tissue can be a complication occurring shortly after therapy or years posttherapy. Frequently, radionecrosis is associated with severe pain and malfunction. Healing is characteristically very slow, requiring months or even years of cleansing and debridement with loss of function and/or cosmetic deformity. These relatively avascular wounds rarely successfully receive tissue grafts and surgical reconstruction is frequently prolonged, requiring multiple staged operations.

During the past ten years several investigators have demonstrated that wounds, especially chronic wounds, exhibit zones of hypoxia and that oxygen is a major factor influencing healing and enhancing leukocyte bactericidal activity and resistance to infection.[1-7] Hunt and his coworkers[1-4] plus other investigators[8-11] have also investigated the mechanisms of oxygen enhancement of wound healing. From these studies, Hunt and his colleagues have proposed that the reparative process in the heal-

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ing of wounds is dependent upon the development of new vasculature to supply the new tissue necessary to fill wound dead spaces. Such new vasculature, however, cannot develop without additional connective tissue support. The formation of a new connective tissue matrix requires increased fibroblastic activity and the synthesis of new collagen which, in the hypoxic areas of the wound, are stimulated by increases in oxygen supply. Capillary buds then grow into this new connective tissue matrix and a new capillary system is established. The resulting advancing vascular and oxygen supplies stimulate further fibroblastic activity, with subsequent obliteration of dead space. In chronic, radionecrotic wounds, greater and more extensive hypoxia exists; collagen production with neovascularization is less active than that present in acute, well-vascularized wounds. Thus, increasing the oxygen supply by hyperbaric oxygen to the relatively avascular, hypoxic areas of radionecrotic wounds results in a stimulation of collagen production and neovascularization with subsequent enhancement of healing.

Further support of Hunt's theory is found in the observations of Kivisaari and Niinikoski[12] that hyperbaric oxygen therapy has little effect on the healing of full thickness, rat skin wounds with intact circulation. However, devascularized wounds with retarded healing were noted to have a normal healing rate in rats treated by hyperbaric oxygen. Also, Greenwood and Gilchrist[13] investigated the degree of flap necrosis in previously irradiated rat skin flaps. Those animals treated with hyperbaric oxygen therapy were noted to have a mean percentage of flap necrosis less than half that found in the irradiated flaps of the control, nonhyperbaric oxygen treated animals.

Several investigators have reported beneficial results with hyperbaric oxygen therapy in the management of human radiation necrosis. Greenwood and Gilchrist[14] noted beneficial results in four patients with radiation necrosis after total laryngectomy. Mainous and Hart[15] reported very successful results using hyperbaric oxygen therapy as an adjunctive modality in the surgical and medical management of 14 cases of refractory osteoradionecrosis of the mandible. These same investigators[16] again reported successful results in the use of hyperbaric oxygen therapy as an adjunctive treatment measure in the management of osteoradionecrosis and soft tissue radionecrosis in various sites in 69 patients. Davis et al,[17] using hyperbaric oxygen as an adjunctive therapy, recently reported healing in 19 of 23 cases of mandibular radionecrosis and in 15 of 16 cases of soft tissue, head and neck radionecrosis. Because of these reports a pilot study was begun at our institution to investigate the effects of hyperbaric oxygen therapy in the management of radiation necrosis.

METHODS AND MATERIALS

Patients were considered for adjunctive hyperbaric oxygen therapy who had received at least 4500 rads of radiation therapy for malignancy and who exhibited necrosis and chronic nonhealing wounds of bone and/or soft tissue in the area of the previous radiation therapy. All patients accepted for treatment must have exhibited radiation necrosis for at least three months with no improvement in spite of adequate nonhyperbaric oxygen therapy. Thus, each patient acted as his own control. No patient was accepted for treatment who had evidence of recurrent or persistent local tumor or evidence of metastatic tumor. Recent biopsies were required in all cases. Complete radiation therapy data were available on each patient. No patients who exhibited medical contraindications to hyperbaric oxygen therapy such as seizures, severe emphysema, asthma, or active alcoholism were accepted for this pilot treatment program.

After complete history, physical examination and laboratory investigations including chest x-rays, EKG and blood chemistry studies, eligible patients were entered into the protocol study after informed consent was obtained. All nonhyperbaric oxygen treatments such as indicated debridement, oral and dental care, analgesics and antibiotics as needed were continued. Hyperbaric oxygen therapy consisted of daily two-hour exposures to pressures of two atmospheres absolute, equivalent to a sea depth of 10.32 meters (33 feet), breathing 100% oxygen. These exposures continued for 40 treatments, given once daily, six days per week. After completion of 40 treatments, an additional 10 to 40 exposures were given after a one to seven-month interruption if complete and persistent healing of soft tissue defects had not occurred. This interruption was instituted in order to avoid pulmonary oxygen toxicity. Periodic follow-up checks at 2 to 12-week in-

TABLE 1. MANDIBULAR RADIONECROSIS AND HYPERBARIC OXYGEN THERAPY (HbO$_2$)

Patient No.	*Radionecrosis Site and Lesion*	*Duration of Radionecrosis Before HbO$_2$ Rx (mo)*	*HbO$_2$ Rx (No.)*	*Improvement in Pain*	*Improvement in Soft Tissue Disease*	*Improvement in X-ray Changes*	*Time Since Last HbO$_2$ Rx (mo)*
1	M+N+F	3	60	Mod	H	Mod	25
2	M+N+F	3	59	Mod	H	O	R tumor - neck - 2 mo - died
3	M	3½	60	Ma	H	Mod	24
4	M+F+Fx	3	60	Ma	H	Mod	27
5	M+Fx	3½	60	Sl	H	Sl	22
6	M+Fx	3	50	Mod	Mod	Sl	R tumor - base of tongue - 1 mo - died
7	M	5	60	Ma	H	Mod	20
8	M+F+Fx	6	80	Ma	H	Mod	11
9	M	6	80	Mod	H-R-H-R	O	6
10	M	6	40	Ma	H	Mod	11
11	M	14	40	N.A.	Ma	Sl	7
12	M	16	40	N.A.	Ma	Sl	5½
13	Mx+M+Fx	5	100	Ma	H-R-Mod	O	1

TABLE 3. RADIONECROSIS IN OTHER SITES AND HYPERBARIC OXYGEN THERAPY (HbO$_2$)

14	Larynx	10	40	Ma	Mod	N.A.	18
15	Nose	60	80	Sl	Sl-grafted-R	Sl	4
16	Floor of mouth	3	40	Ma	Ma	N.A.	1
17	Vagina	10	40	Ma	H	N.A.	24
18	Foot	8	80	Mod	Sl	O	11 - R tumor in lesion
19	Hip and femur	8	40	Sl	O	O	8 - pulmonary metastasis

M - Mandible; N - Neck; F - Fistula; Fx - Fracture; Mx - Maxilla; Sl - Slight; Mod - Moderate; Ma - Marked; H - Completely healed; R - Recurred; HRHR - Healed-Recurred-Healed with retreatment - Recurred; HR-Mod - Healed-Recurred-Moderate improvement with retreatment; O - No improvement; N.A. - Not applicable-findings not present before HbO$_2$ treatment.

TABLE 2. HYPERBARIC OXYGEN THERAPY MANDIBULAR OSTEORADIONECROSIS

	No. of Cases	*Supplementary Information*
Total number of cases	13	40 to 100 treatments completed (1 - maxilla and mandible, 12 - mandible)
Times since last treatment (1-27 months)		
Relief of pain		
Marked	6	
Moderate	4	
Slight	1	(2 cases did not have significant pretreatment pain)
Improvement in soft tissue disease	7	Complete healing — 11-27 months posttreatment (6 required more than 40 treatments)
	2	Complete healing then recurrence of radionecrosis 6 mo and 9 mo posttreatment
	1	Complete healing then recurrent cancer 2 mo posttreatment
	3	Improved but did not completely heal (1 died of recurrent tumor, 2 have received only 40 treatments)
Radiographic improvement	10	Slight to moderate improvement
	3	No improvement (1 case improved but recurred)

tervals after completion of hyperbaric oxygen therapy were performed. Recurrent lesions were biopsied and if tumor was found, hyperbaric oxygen therapy was discontinued and additional cancer therapy was begun.

Hyperbaric oxygen was administered by a clear plastic head tent connected to a closed circuit, a carbon dioxide absorbent breathing system containing 100% oxygen located in a multiplace chamber compressed with air. Oxygen content of the head-tent gas was continuously monitored during treatment and was found to be 98% or greater. Chamber oxygen content was also monitored and kept below 21% in order to minimize fire hazard. During treatment, all patients were attended by a diving technician in the chamber as well as an outside chamber operator and technician.

X-rays of bone radionecrosis and photographs of soft tissue lesions were obtained before and after each cycle of 40 treatments and at three to six-month intervals during posttreatment follow-up periods. Sizes of soft tissue lesions and degrees of pain relief were observed and documented at frequent intervals.

RESULTS

Mandibular Radionecrosis (Tables 1 and 2). A total of 13 patients with mandibular radionecrosis have completed at least one course of 40 hyperbaric oxygen treatments since the fall of 1975 (Tables 1 and 2). All patients had radiographic evidence of mandibular radionecrosis with soft tissue breakdown and intraoral bone exposures. Four cases in addition had orocutaneous fistulas and five exhibited pathologic fractures. Severe pain was present in 11 cases. These signs had been present for 3 to 16 months prior to hyperbaric therapy with no evidence of improvement in any case in spite of adequate nonhyperbaric oxygen therapy. Ages ranged from 43 to 68 years. Time since completion of radiation therapy before beginning hyperbaric oxygen therapy ranged from five months to 22 years. Ten patients were from 3 to 36-months postoperative head and neck cancer surgery procedures. All patients exhibited at least one of the indications (intractable pain, fistula, fracture, or nonhealing after 12 months of therapy) for hemimandibulectomy as defined by Rankow and Weissman.[18] Time of follow-up since the last hyperbaric oxygen treatment at the time of this reporting ranges from one to 27 months. No patient thus far has undergone a hemimandibulectomy or surgery other than sequestrectomy.

Of the 11 cases with significant pretreatment pain, all showed varying degrees of pain relief with marked relief in 6 cases, moderate relief in 4 cases, and slight relief in one case. Two patients did not have significant pretreat-

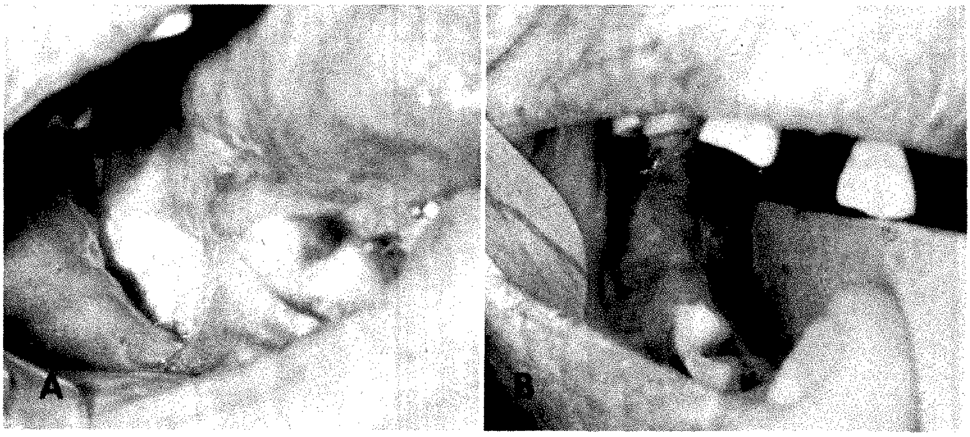

Fig. 1. A) Patient No. 10 before hyperbaric oxygen treatment, showing intraoral bone exposure over right mandibular ramus. B) Same patient three months after completion of 40 hyperbaric oxygen treatments, showing complete mucosal healing.

ment pain. The judgment of pain relief, if present, was based on the subjective physician, nursing and chamber staff impressions, plus the frequency of the need for pain medication. The majority of pain relief appeared to occur within the first 20 hyperbaric oxygen treatments; in some cases significant pain relief occurred after 12 treatments, similar to the observations of Davis et al.[17]

Improvement in soft tissue disease was judged by the observation of intraoral mucosal defects, bone exposures, and draining orocutaneous fistulas. Complete healing of soft tissue disease which has persisted from 11 to 27 months was noted in seven cases (Nos. 1, 3-5, 7, 8, 10) (Fig. 1A, B). Six of these cases required more than 40 treatments to achieve this result. Complete healing of soft tissue disease was also noted in three additional patients. Patient No. 2 was noted to heal completely during 59 treatments, but he developed recurrent cancer in a site distant from the radionecrotic area two months after completion of hyperbaric oxygen therapy and subsequently died of cancer. Healing of the radionecrotic lesion persisted until death. Patient No. 9 completely healed during the first course of 40 treatments only to suffer partial recurrence of the lesion two months posttreatment. The lesion rehealed with a second course of 40 treatments and remained healed for six months posttreatment. It has recently partially recurred and the patient is scheduled for another course of treatment. Patient No. 13 initially developed posterior maxilla and mandibular coronoid process radionecrosis with intraoral bone exposure and with marked pain and trismus. After 60 hyperbaric oxygen treatments, complete intraoral healing with a significant reduction in trismus and an absence of pain was noted. Radiographs indicated increased bone deposition in the involved area. Nine months later, this patient developed a recurrence of radionecrosis in the maxilla and mandible with a pathologic fracture of the coronoid process and with two draining cutaneous sinuses. He has just completed an additional 40 hyperbaric oxygen treatments and has noted a marked reduction of pain, a slight reduction in trismus, and decreases in the size of intraoral bone exposures and in the amount of skin drainage. Additional therapy is planned.

Three other cases (Nos. 6, 11, and 12) noted improvement but incomplete healing of soft tissue disease. One of these patients (No. 6) developed a recurrence of her base of tongue carcinoma one month after completion of 50 hyperbaric oxygen treatments with a decrease in size of intraoral bone exposure and fracture union during treatment. She later died of cancer and healing of radionecrosis remained incom-

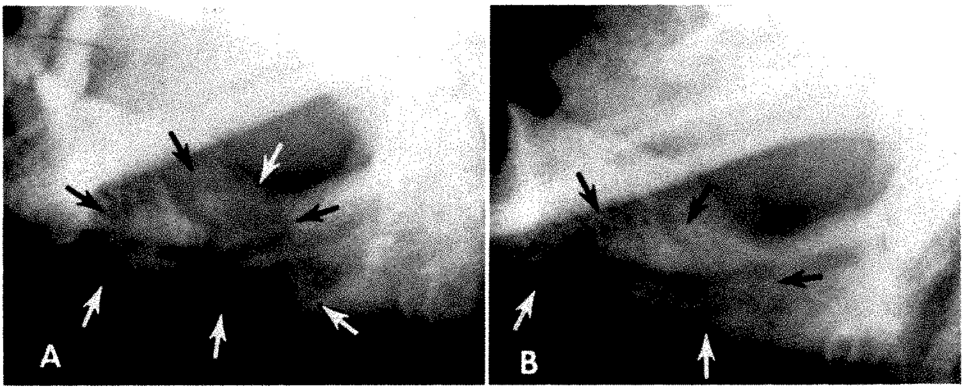

Fig. 2. A) X-ray of patient No. 10 before hyperbaric oxygen treatment, showing radionecrosis of right mandibular ramus. B) Same patient 11 months after completion of 40 hyperbaric oxygen treatments, showing increased bone deposition and resolution of previous radiolucent areas.

plete. Two patients (Nos. 11 and 12) have completed only 40 hyperbaric oxygen treatments and are scheduled for second treatment courses.

Radiographic improvement in the osteoradionecrosis lesions was noted to be slight to moderate in degree in ten cases. The improvements seen were mainly manifested by smoothing and more regularity to irregular scalloped edges of bone breakdown plus increased bone deposition (Fig. 2A, B). These changes, when noted, appeared late and were not detected in any patient before four months after the initiation of hyperbaric oxygen therapy. Two cases, (Nos. 2 and 9) as described above, did not exhibit radiographic improvement even though soft tissue disease did improve. Case No. 13, also described above, initially exhibited increased bone deposition with complete healing after 60 hyperbaric oxygen treatments. When signs of radionecrosis appeared nine months later, radiographs demonstrated more extensive areas of necrosis plus a fracture of the coronoid process. He thus far has shown no radiographic improvement.

Radionecrosis in Other Sites (Table 3). One patient (No. 15) was treated with radionecrosis of bone and soft tissue of the nasal bridge. She had exhibited this problem for ten years after receiving x-ray radiation therapy for treatment of an ethmoid tumor. She has now completed 80 treatments, and posttreatment radiographs have shown increased density in the involved nasal bones. A posttreatment attempt at surgical closure with an island forehead flap was a partial failure. The remaining exposed area has just been closed with a skin graft.

Another patient (No. 16) has just completed 40 hyperbaric oxygen treatments for postoperative radionecrosis of the floor of the mouth. Mandibular radionecrosis has not been thus far demonstrated. He has noted marked pain relief with 90% healing of the soft tissue disease.

An additional case of radionecrosis of the larynx (No. 14) was given 40 hyperbaric oxygen treatments with resulting significant improvement in pain and a decrease in size of the laryngocutaneous fistula. He did not completely heal and does not wish further treatment.

Three other patients with radionecrosis of the foot (No. 18), hip (No. 19), and vagina (No. 17) have been treated with at least 40 treatments. Results in the vaginal case were excellent with complete healing and relief of pain. The other two patients had only minimal improvement in soft tissue disease and no radiographic improvement in bone changes. Each developed recurrent or metastatic tumor one month and three months after treatment had ended.

Thus far, 1,109 hyperbaric oxygen treatments have been given to the 19 patients described above. No major complications of compressed gas exposure have been noted. Tympanostomy tubes were required in four patients for adequate middle ear pressure equalization during compression. No complications of this procedure were experienced.

Approximately one year after the study began, blurring of distant vision, myopia, was noted in several patients after approximately 20 to 24 hyperbaric oxygen treatments. Inquiry with investigators in this field revealed that similar changes had been noted in some of their patients; however, the loss of far visual acuity usually subsided with a return to pretreatment vision three to four weeks after hyperbaric oxygen treatments had ended. Upon noting this phenomenon we began to perform visual studies with colleagues in the Department of Ophthalmology on the ten patients entered into the study since this observation. Myopia has been noted to develop in eight of the ten patients thus far studied. Thus far, all patients have shown a return to pretreatment visual levels within three months after exposure. Ocular studies have shown no significant changes in corneal curvature, intraocular pressure, lens appearance, accommodative spasm, lens clarity, retinal appearance, or anterior-posterior (axial) length of the globe. The myopia is postulated to be the result of an, as yet unexplained, increase in convexity of the lens which gradually disappears after discontinuing the daily hyperbaric oxygen exposures.

DISCUSSION

The results of this pilot study are in general agreement with those of other authors[14-17] and indicate that hyperbaric oxygen is a beneficial adjunctive treatment modality in the management of radiation necrosis of bone and soft tissue, particularly of the head and neck. Hyperbaric oxygen therapy should be considered an adjunctive treatment modality in the management of radionecrosis: indicated and needed surgical debridement of obviously nonviable tissue, hygiene, cleansing, and antibiotic care must continue. The observation of complete and persistent soft tissue healing thus far in 7 of 13 cases of mandibular radionecrosis which exhibited one or more of the previously published criteria for hemimandibulectomy[18] suggests that the need for vigorous debridement to grossly bleeding tissue, with the subsequent loss of potentially viable bone and soft tissue, can be significantly lessened with the use of hyperbaric oxygen. The impressive relief in pain noted in this study and by Davis et al[17] supports the use of this treatment modality for refractory radionecrosis.

This study does not answer the question of whether 100% oxygen administered at atmospheric pressure would be just as efficacious in the treatment of radionecrosis. Animal studies quoted previously[1,12,13] suggest that oxygen levels in the hypoxic areas of chronic wounds need to approach 24 to 30 mm Hg for optimal collagen production and neovascularization and that hyperbaric oxygen is usually necessary to achieve such a result. Also, verbal reports of a double blind control study at another institution[19] indicate that patients treated with hyperbaric oxygen exhibit improved and more rapid healing of radionecrotic lesions than those patients treated with 100% oxygen at atmospheric pressures.

In the management of radionecrosis with hyperbaric oxygen, the optimum pressures, times of exposure, and frequency plus number of treatments have not been established. Our treatment schedule was chosen to avoid pulmonary and cerebral oxygen toxicity and to follow that of other investigators.[15,16] Davis et al[17] followed a different treatment schedule using higher pressures with intermittent oxygen and air breathing for shorter times with fewer exposures. Their results appear to be just as good, if not better, than those reported in this study. However, patients in this study were not required to exhibit nonhealing for at least three months prior to hyperbaric oxygen therapy. Further investigations with measurements of oxygen tension in different areas of various types of wounds are needed.

Previous animal and human studies[2,3,5,12,13] have shown that hyperbaric oxygen therapy will not compensate for a complete absence of blood supply in wound healing and that the response will depend upon the degree of wound ischemia. Chronic radionecrosis wounds exhibit various degrees of ischemia and hypoxia in different locations of the wound. Apparently, hyperbaric oxygen therapy for those wounds with major vascular supplies intact, but with reduced small arteriolar and capillary blood supplies, results in increased fibroblastic activity and neovasculation in the previously hypoxic areas of the wound with subsequent enhancement of healing.

In this study only patients who had exhibited radionecrosis for at least three months with no significant improvement in spite of adequate nonhyperbaric oxygen therapy were included. Thus, the efficacy of initiating this form of therapy earlier in the postoperative period for those irradiated patients who begin to exhibit signs of wound breakdown, or even before signs of wound breakdown in such patients, is not answered by this study. The experience of Davis et al[17] suggests that hyperbaric oxygen therapy is beneficial when initiated as soon as signs of inadequate healing appear in the postoperative period in previously irradiated patients.

Hyperbaric oxygen therapy for radionecrosis is a potentially expensive and complex form of treatment which requires careful patient selection, adequate and safe pressure facilities, and a technical and medical staff with previous formal training and experience in operating such facilities. Exposure to high pressures of oxygen can result in serious complications, such as pulmonary and cerebral oxygen toxicity, air embolism, decompression sickness, and pneumothorax. In each case, the potential risks of such therapy must be carefully weighed against the possible benefits. Experience at our institution and elsewhere suggests that when well-established standards of hyperbaric chamber practice[20] are followed, such therapy can be administered safely with an extremely low incidence of serious complications.

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XII WORLD CONGRESS OF OTORHINOLARYNGOLOGY

The XII World Congress of Otorhinolaryngology will be held June 21-26, 1981 in Budapest, Hungary. Preliminary communications, recommendations and suggestions, should be directed to Prof. Dr. L. Surján, President, XII World Congress of ORL, H-1389 Budapest, Pf: 112 Hungary.

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SURGICAL TREATMENT OF ACUTE BLUNT LARYNGEAL INJURIES

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The best management of acute laryngeal fractures is an approach which promotes healing by primary intention and does not require the use of a lumen keeper or core mold. This presentation outlines the theoretical considerations and practical steps which make it possible to achieve these goals. The basic emphasis is on proper diagnosis, good surgical exposure and proper wound management. Also included are some ideas about the special anatomical and physiological characteristics of the larynx which make it difficult to obtain primary healing. The material presented is a synthesis of pertinent basic laryngologic research, wound healing theory and clinical experience.

Laryngologists have long warned that persons sustaining severe acute laryngeal injuries must be diagnosed early and treated by a specialist. However, the literature to date fails to define a consistent and reliable surgical approach for obtaining optimum results in the repair of such injuries. The goal of this presentation is to describe my approach to diagnosis and treatment, explaining some new concepts and procedures which I find very useful.

DIAGNOSIS

Signs and Symptoms. The signs and symptoms of blunt or penetrating injury to the neck involving the larynx are well-known to the laryngologist. They include subcutaneous emphysema, hoarseness, hemoptysis, airway obstruction, painful swallowing, loss of the laryngeal prominence, etc. Injury to the cervical spine may cause the patient great pain with attempts at moving or turning the head.

Examination. The single most valuable diagnostic technique available is mirror examination of the larynx. This method is least likely to precipitate an emergency in someone who is partially obstructed. It can be done quickly and without special preparation. The type of view obtained with the mirror is more comprehensive and less distorted than the view with a direct laryngoscope.

X-rays are of considerable value as well. The most helpful views are the lateral soft tissue, A-P laminograms, and xerograms. X-rays are most valuable for evaluation of the subglottic region.

Direct laryngoscopy has some drawbacks as a diagnostic procedure in these patients. In someone with a freshly injured larynx it could precipitate obstruction and tracheotomy. Also, the scope gives a limited view and introduces distortion of its own. If the patient obviously has a severe injury and already has a tracheotomy, a direct laryngoscopy will of course be part of the workup. In less severe injuries not requiring tracheotomy, and especially if the larynx can be viewed with a mirror, direct laryngoscopy may not be required at all.

Diagnosis can be unusually difficult in a patient who has sustained a cervical spine fracture and been placed in traction. In these patients, direct laryngoscopy is usually impossible. Indirect laryngoscopy may precipitate gagging and undesirable stress on the neck injury. In such patients, it may be possible to use a flexible laryngoscope with fiberoptic lighting. If this cannot be done, a laryngotomy may actually be required

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before one can be sure of the severity of the injury. Because of the high priority to be placed on early diagnosis in these patients, I feel the laryngotomy in such a situation is justified.

Prognosis. My experience[1] has shown that the most important prognostic signs in acute blunt laryngeal injuries are:

1. Immediate or very early airway obstruction requiring tracheotomy. When an early tracheotomy is required to save the life, the lumen of the larynx has usually been severely compromised by skeletal collapse.

2. The presence of bare cartilage edges or surfaces in the lumen of the larynx is an extremely bad prognostic sign. The cartilage behaves poorly because of its avascular nature. Fibrosis and granulation around exposed cartilage is excessive.

3. Fracture and collapse of the cricoid is the third important feature indicating a poor prognosis.

These three findings, then, are usually associated with an unfavorable outcome unless aggressive treatment is used. The rest of this presentation is a description of the "state of the art" as I see it for the surgical treatment of severe acute blunt laryngeal injuries.

BASIC PRINCIPLES OF REPAIR

One should repair these injuries as soon as possible. There are, however, reasons why one may have to wait. First of all, diagnosis is easier after three or four days have passed and some of the swelling has gone down. Secondly, in some of these injuries, the patient is so severely injured that immediate repair of the larynx cannot be done. If the repair is delayed for any reason, it may be helpful to place the patient on steroids. They delay wound healing, so that granulation tissue and collagen deposition will not occur during the period before the wound is definitively treated. If this is done an anatomic repair is facilitated.

In reviewing wound healing principles[2,3] it soon becomes obvious that what is needed in these severe injuries is healing by *primary* intention. We are searching here for a technique which will give us the equivalent of the "fine scar" which is the ultimate goal of the cosmetic surgeon. In the case of laryngeal fractures, the fine scar has great functional importance and if ever the surgeon needed it, this is the place. Unfortunately, much modern thinking on this subject has stressed the use of methods which require healing by *secondary* intention. For example, the placement of a lumen-keeper by endoscopic means is a method which does not allow the surgeon to close mucosal lacerations or anatomically reduce skeletal fractures. As such, it requires that healing be by secondary intention in some areas of the wound. Unfortunately, in any system where healing is by secondary intention, there will be greater deposition of collagen scar than in primary healing. In the larynx this will lead to a number of undesirable effects, the worst of which is the stenosis of the lumen in the long run.

There are good reasons why healing by primary intention in the larynx is difficult to achieve, and I list four of them:

1. There is a great deal of mobility in some parts of the larynx and laryngopharynx. In such mobile areas, mucous membrane has a very thin or absent submucosa. Repairs of mucosal tears or lacerations do not hold well in this tissue.

2. Severe blunt or lacerating injuries of the laryngeal area may result in a loss of skeletal, connective tissue or muscular support in the zone of injury. With each swallow, the larynx is drawn upward with some force. If part of the structure is weakened by the injury, it will tend to be stretched and pulled apart. This results in narrowing, and places undue tension on the surgical repair.

3. Cartilage lacks a blood supply and tends to behave like a foreign body causing excessive and prolonged granulation and collagen tissue deposition. Not only does exposed cartilage delay healing but it may be absorbed in the course of healing because of infection

and exposure with loss of skeletal support of the laryngeal lumen, compounding the problem.

4. Last but not least, the mobility of the larynx during side to side motions and extension and flexion of the head is very great. With all of this motion, it is very difficult to put the structures that have been injured at rest during the healing period.

In an effort to control healing and promote primary healing, I have tried to devise methods of dealing with each of these problems of wound healing in the larynx. The methods which I list here constitute a rational and systematic approach to acute laryngeal injuries.

Antibiotic Prophylaxis. The accumulated evidence[4] appears to favor the use of antibiotic prophylaxis in wounds and surgery involving the mucous membrane. The antibiotic may also improve the tolerance of the larynx to a stent in case one must be used.

Steroids. The function of steroids in the acute injury is to delay healing until definitive treatment can be undertaken. After surgical repair they should be omitted because they interfere with healing. Since the goal in this scheme is to achieve rapid, prompt and primary healing, any interference with this process must be minimized.

Open Repair. Surgeons dealing with the problem of acute laryngeal injuries have frequently recommended procedures which are "closed" or are performed endoscopically. The main reason for this is that open surgical exploration of the larynx may cause damage, making the situation worse instead of better. I believe the opposite is true. The only way that one can obtain primary healing and correctly reduce a fracture of the laryngeal skeleton is by an open procedure. If an open procedure has a small or even a significant effect on voice, but eventually allows decannulation, the correct course has been chosen. I also feel, however, that a properly done laryngotomy need not interfere with voice or create any greater risk of stenosis. A vertical incision of the airway can be done from the hyoid to the trachea without fear as long as the closure is careful and anatomic. In order to improve surgical exposure and to minimize exposure of cartilage to the wound, I recommend angling off center above the anterior commissure parallel to the inferior-lateral margin of the epiglottis. This procedure allows one to incise the entire aryepiglottic fold on one side or the other and gain significant improvement in exposure. This method also preserves epiglottic mucosa for a flap or graft if one should be needed (Fig. 1).

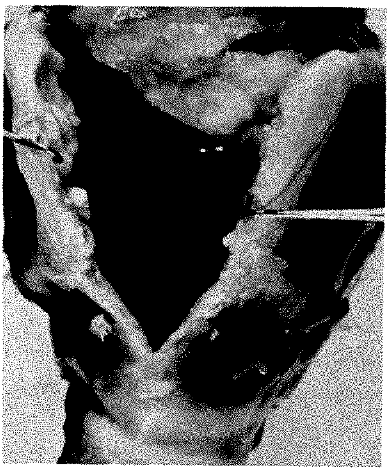

Fig. 1. Cadaver larynx showing the exposure obtained by cutting through the aryepiglottic fold on one side.

Double Epithelial Coverage. When repairing these injuries, all epithelium is saved. Mucous membrane tears must be sutured carefully and if mucosa is lost, flaps must be swung wherever possible. If no flap material is available and if mucosa is lost, one can graft with free mucosal grafts taken from the epiglottis or from other parts of the body such as the buccal area of the mouth.

Because of the poor quality of the submucosa in the larynx, and because of the mobility of the area there will usually be separation of mucosal repairs. For this reason, I have adopted the practice, advocated by Harris et al[5] of skin grafting the lumen over a soft sponge stent. With the graft in place, raw areas that may develop during healing will be epithelialized with skin. Ex-

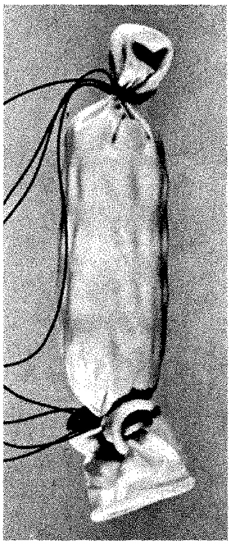

Fig. 2. Soft laryngeal stent. Three finger cots cover an appropriately sized piece of sponge rubber. The silks are tied around the rubber and left long for fixation of the stent. The stent is completed by suturing a skin graft, raw side out, on it.

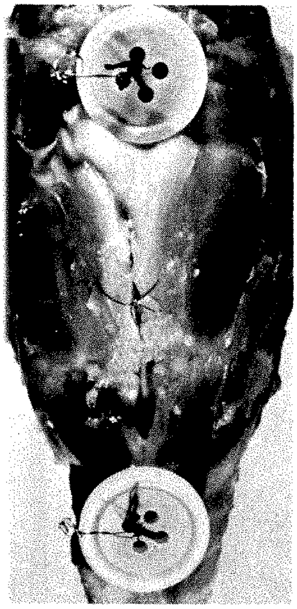

Fig. 3. Cadaver larynx showing method of stent fixation. Silk sutures from the stent (see Fig. 2) are tied to buttons. Wires looped through the buttons are led out through the skin to facilitate removal of the buttons.

cess skin will slough in a few days. My experience has been that in most acute injuries treated this way, small areas of skin will take. Were it not for these skin grafts, areas of suture line breakdown would have to heal by secondary intention which usually leads to some reduction of lumen size.

Soft Stent. In placing a skin graft in the larynx, a soft, yielding stent is essential because of the motion which is inevitable in this area. The construction of the stent is as described by Harris et al.[5] A piece of sponge rubber, either artificial or natural, is cut to fit the lumen of the larynx. It is covered by two or three layers of finger cot or glove fingers which are tied tightly at each end with silk. There must be no openings in the rubber. The silk is left long and used for retention of the stent (Fig. 2). A skin graft, cut .25 to .375 mm in thickness, is sutured over the stent, raw side out, using fine plain catgut. This assembly is placed in the lumen of the larynx and is secured by passing the silk sutures out through the trachea or the cricothyroid membrane below and through the thyrohyoid membrane or base of tongue above. After closure of the larynx, the sutures are placed through the holes in metal or pearl buttons at the level of the strap muscles rather than at the level of the skin. A pull-out wire is also placed through the button holes and this is lead out through the skin and allowed to hang loose outside the surface. The retention buttons are placed deep in the tissue so that they will move precisely with the larynx as it moves up and down with swallowing (Figs. 3 and 4). This stent can be removed about seven to ten days after placement. The button is pulled up using the wire and is exposed by a small skin incision. The silk is cut, releasing the stent which is then removed with a laryngeal forcep through the laryngoscope.

Dressing Skin Graft. A second theoretical advantage of the skin graft is that the skin covering the stent may prove to be a well-tolerated surface to place against the intact mucosa. The concept is that those areas of skin graft

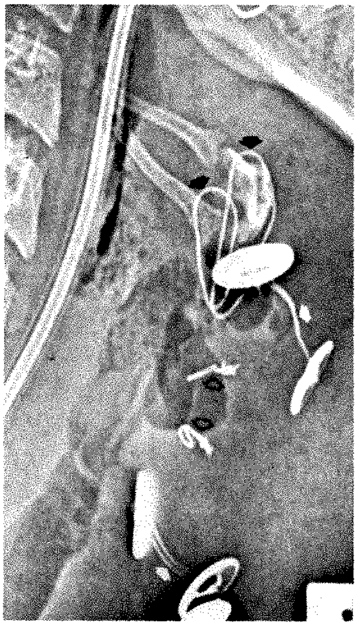

Fig. 4. Xerogram of stent in position. Two suspensory wires (black arrows) are present between hyoid bone and thyroid cartilage. Two wires (open arrows) close the thyrotomy incision. Pull-out wires (white arrows) lead from the retention buttons to small buttons near the surface of the skin. A feeding tube is in the pharynx.

which are not required to heal the wound will slough gradually over the first week, providing a liquid, mobile interface between larynx and stent, one which does little or no damage to the intact mucosa of the larynx. The skin graft then may be thought of as serving a dual purpose, as graft and as dressing.

Skeletal Reduction. Direct repair of the laryngeal skeleton following fracture is an essential feature of any system to restore the lumen of the airway. The airway has an exoskeleton which gives it support. If one can stiffen and restore this structure, it will provide resistance against contraction of scars in the lumen. The only way to thoroughly reduce and restore the skeleton of the larynx is by direct exposure of the fractures and direct wiring.

Laryngeal Suspension. The problem of stretching and elongation of the larynx following trauma because of swallowing can be counteracted by suspending the larynx much as one suspends a facial fracture.[6] This is accomplished by placing wires from the first intact point above the fracture, usually the hyoid bone, to the first undamaged structure below the injury. This might be the thyroid, cricoid or tracheal cartilages. When this has been done, upward force on the hyoid will be transmitted through the wires, preventing distraction of repaired laryngeal cartilages and soft tissues.

No Lumen Keeper. In my opinion, there is ample evidence in the wound healing and laryngological literature[7] that long term lumen keepers do more harm than they do good. If the laryngeal wound has been properly managed and if the stent and skin graft have been properly applied, there will be no significant granulations anywhere within the lumen of the larynx. In my experience, the only granulation will be at the point where the silk sutures holding the stent in place exit the larynx. Thus, when the sponge stent which holds the skin graft has been removed, the surgical treatment program ends. If stenosis recurs following this, I believe the best course is to start over on this same type of program rather than placing a lumen keeper in the larynx.

OPERATIVE MANAGEMENT

The principles outlined above can be translated into a step-by-step action program which can be used in most every case of severe injury.

1. Begin penicillin or erthyromycin before surgery.

2. The "T" skin incision gives the best exposure with the least flap elevation and retraction. A horizontal incision can also be used.

3. Separate the strap muscles from hyoid to trachea and elevate laterally as needed to see any damage to cricoid and thyroid cartilages. It is often necessary to free sternohyoid and thyrohyoid from the hyoid bone. Do not wire fractures at this time.

4. Make a shallow horizontal saw cut

in the thyroid cartilages to help restore normal alignment when closing, then separate the thyroid cartilage vertically in the midline with an oscillating saw. Do not enter the lumen.

5. Incise cricothyroid membrane vertically in the midline until the lumen is opened.

6. Using a scissor cut through the anterior commissure exactly in the midline from below. This can usually be done under direct vision.

7. Above the glottis, the incision angles right or left of the epiglottis to avoid cutting into the cartilage or its mucosa. Extend this incision until exposure is adequate. It may be extended all the way through the aryepiglottic fold, if necessary.

8. Be careful to avoid injury to the internal branch of the superior laryngeal nerve.

9. Debride where necessary; develop mucosal flaps of epiglottis[6] or pyriform; obtain free mucosal grafts from cheek or nose if needed; reduce cricothyroid and cricoarytenoid dislocations; suture mucosa and mucosal flaps and grafts meticulously.

10. Prepare and fit a soft stent covered by split thickness skin.

11. Wire the laryngeal cartilage fractures and the midline cartilage incision. Use fine wire and small drill holes. Use figure of "8" with the wires crossed between cartilage fragments to prevent overriding.

12. "Suspend" the larynx by placing wires between the hyoid and some point below the level of repair. Pull up a little in order to shorten and widen the lumen and take all tension off the repair. These wires need not be removed.

13. Place buttons above and below to hold stent in position. Place pull-out wires in the buttons and lead them out through the skin. Close the incision.

14. Continue low dose prophylactic antibiotics while stent is in place. Do not use steroids.

15. In seven to ten days return to O.R.; pull up buttons and cut down on them; sever the sutures holding the stent. Pull out the stent endoscopically.

SUMMARY

In this paper I have tried to bring together all the best available information on repair of severe, acute, laryngeal injuries. The conclusions I have reached are based on animal research,[8] wound healing theory and observation of clinical cases. These techniques have proven invaluable to me in managing these patients.

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VOICE SPECTROGRAPHY IN THE EVALUATION OF MYASTHENIA GRAVIS OF THE LARYNX

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Myasthenia gravis is a neuromuscular disorder that affects striated muscles especially those innervated by the cranial nerves. The standard diagnostic regimen is to find a reversal of symptoms by acetylcholine esterase administration. The permanent and objective recording of this effect is the key to an accurate assessment of this test. The voice spectrograph is a noninvasive means of evaluating the voice. It has been used successfully to make a clear and specific diagnosis of myasthenia gravis as it affects the larynx. The test can be used to distinguish myasthenia gravis from other functional, anatomical and neuromuscular laryngeal disorders.

Progressive dysphonia without obvious anatomical lesion or paralysis is a diagnostic problem for the laryngologist. The etiology of this dysphonia runs the gamut from functional disorders to intrinsic disease of the laryngeal musculature. Aronson listed the differential diagnosis of these disorders in his 1971 article.[1] Myasthenia gravis must be distinguished from these other progressive laryngeal disorders.

Myasthenia gravis is a neuromuscular disease characterized by excessive fatigability of muscles that undergo repetitive stimulation or activity. Muscles involved tend to become weaker as the day progresses and improve with rest. The disease affects striated voluntary musculature in different areas to a variable extent. Muscles innervated by the cranial nerves appear to be particularly affected, causing such findings as ptosis and variable ophthalmoplegia. The disease may progress to involve other striated muscles, including limb and bulbar musculature (e.g., swallowing, respiration and phonation).

The pathogenesis of myasthenia gravis is complex. Both presynapic and postsynapic defects of the neuromuscular junction have been described. Present concepts of etiology revolve mainly around immunologic abnormalities of both cell-mediated and humoral varieties. These immunologic abnormalities appear to have their greatest impact at the postsynapic common receptor sites.

Current diagnostic modalities available for myasthenia gravis are divided into electrophysiological and pharmacological tests. In the electromyographic studies, a defect of the neuromuscular junction can be demonstrated by showing fatigue on repetitive electrical stimulation with posttetanic exhaustion and characteristic decremental response. Pharmacologic tests primarily utilize the principle of acetylcholinesterase inhibition. In these tests, the symptoms of myasthenia gravis are reversed, using injections of neostigmine or edrophonium. Clinically, the effect of edrophonium on the involved musculature becomes evident within 10 to 30 seconds and its effects may persist for 120 seconds. It may be used in conjunction with electromyographic testing to show

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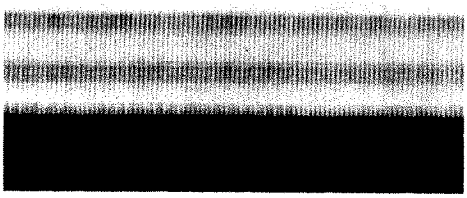

Fig. 1. Normal male spectrogram.

reversal of muscle fatigue following acetylcholinesterase inhibition. The reversal to normal electromyographic testing after its injection is the end point of the test. False positive tests to edrophonium have been reported but are rare. False negative response rates are more common and range between 10-22%.[2,3] It is felt that these are due to the inability to consistently record an objective end point.

Accurate diagnosis of myasthenia gravis involving the larynx is important but is not easily accomplished; as many as 6% of myasthenics present only as dysphonia.[4,5] Although electromyography of the larynx can be performed, it is a tedious and cumbersome procedure and not applicable in a clinical setting. A safe, objective and noninvasive test to determine the end point of the edrophonium test as pertains to the larynx is needed.

In 1969, Maxwell and Locke[6] seemed to be able to discern a change in the voice pitch following injection of edrophonium, but hastened to qualify the results. In 1975 Nieman et al[7] used voice printing to analyze continuous speech for changes in voice patterns. One patient with myasthenia gravis was studied and changes in breathiness and amount of vocal energy were noted.

Neither of these studies addressed themselves to the problem of isolating changes in vocal cord function following edrophonium injection. Previous studies by the authors have shown that vocal function can be clinically analyzed, using the voice spectrograph.[8,9] An accurate assessment of the edrophonium test will promote a satisfactory therapeutic regimen in patients with myasthenia gravis of the larynx.

METHODS AND MATERIALS

In this study, voice production was examined and analyzed by the use of voice spectrography to show how it may objectively demonstrate the effect of the drug on the larynx. The techniques used were identical to those previously described by the authors.[8,9] These involve the use of a high quality cassette audio tape recorder and subsequent spectrographic analysis on the Kay Elemetrics Corporation sonograph.

A baseline recording of the steady state vowel "ah" was made just prior to the edrophonium injection. The patient was then injected with 10 mg of IV edrophonium over a ten-second period. Voice samples were obtained at intervals of 15, 30, 45, 60, 120, 150 and 180 seconds after injection. Broad band spectrographic displays were produced from these recordings and a permanent record was obtained. Each spectrogram was analyzed for changes in periodicity of vocal cord function, formant structure, and breathiness. These characteristics as well as a normal spectrogram are shown in Figures 1 and 2.

The basic parameters of the spectrogram after injection of the edrophonium were compared in timed sequence with the known pharmacologic action of this drug. A positive response in this study was considered to be the occurrence of one or any combination of the following: 1) Significant improvement in periodicity of vocal cord function, 2) Resolution to normal formant structure, and 3) Reduction of breathiness. If a positive response was obtained, the patient was then placed on long-term pyridostigmine therapy (Mestinon®). Follow-up spectrograms after two months of treatment were then obtained and compared to the pre-edrophonium injection voice.

Patients were selected for this study if they satisfied any of the following criteria: 1) Progressive or continued weakness of the voice, 2) Vocal symptoms in addition to other stigmata of myasthenia gravis, and 3) Previous diagnosis of myasthenia gravis now presenting with vocal dysfunction. Each of these patients were examined by a laryngologist, neurologist and speech pathologist.

RESULTS

Case reports on six representative patients are presented to show the effectiveness of voice spectrography in diagnosing myasthenia gravis of the larynx.

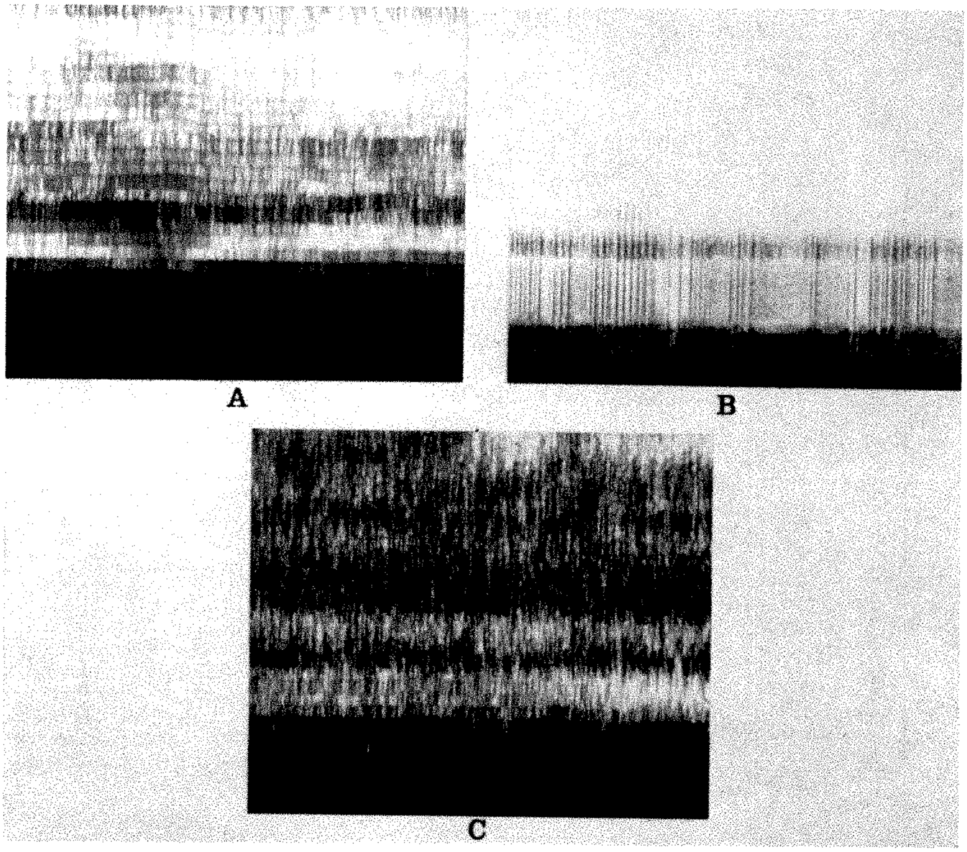

Fig. 2. Examples of spectrographic characteristics of dysphonia. A) Formant breakdown; B) Aperiodicity; C) Breathy quality.

Case 1 (G.W.). This 60-year-old Caucasian female presented with a history of progressive dysphonia. She had noted her voice weakening on prolonged talking and had no other generalized symptoms. In 1956, a diagnosis of myasthenia gravis had been established at the Cleveland Clinic. The patient had been on medication following that original diagnosis and had done fairly well. Five years prior to this visit, her symptoms had abated and she was removed from medication. She had no other symptoms prior to this intermittent hoarseness and dysphagia.

A neurological examination revealed a mild ptosis of the left eyelid with repetitive upward stimulation as well as subjective diplopia on sustained lateral gaze to the left. Laryngeal examination was normal. The patient underwent the Tensilon®*-Spectrographic-Test (TST) (Fig. 3). The preinjection state is represented by noticeable aperiodicity of vocal movement with intermittent normal phonation. There was no evidence of breathiness. The 30-second postinjection spectrogram showed improvement in all aspects of the aperiodic condition. The spectrogram representing the patient's voice after being placed on pyridostigmine showed good response in formant structure with no evidence of aperiodicity.

Case 2 (I.H.). This 71-year-old Caucasian female presented in July, 1977 with dysphonia associated with generalized fatigue. A previous diagnosis of ocular myasthenia gravis had been made in 1971. The patient was placed on

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*Tensilon® (edrophonium). Roche Laboratories, Nutley, NJ.

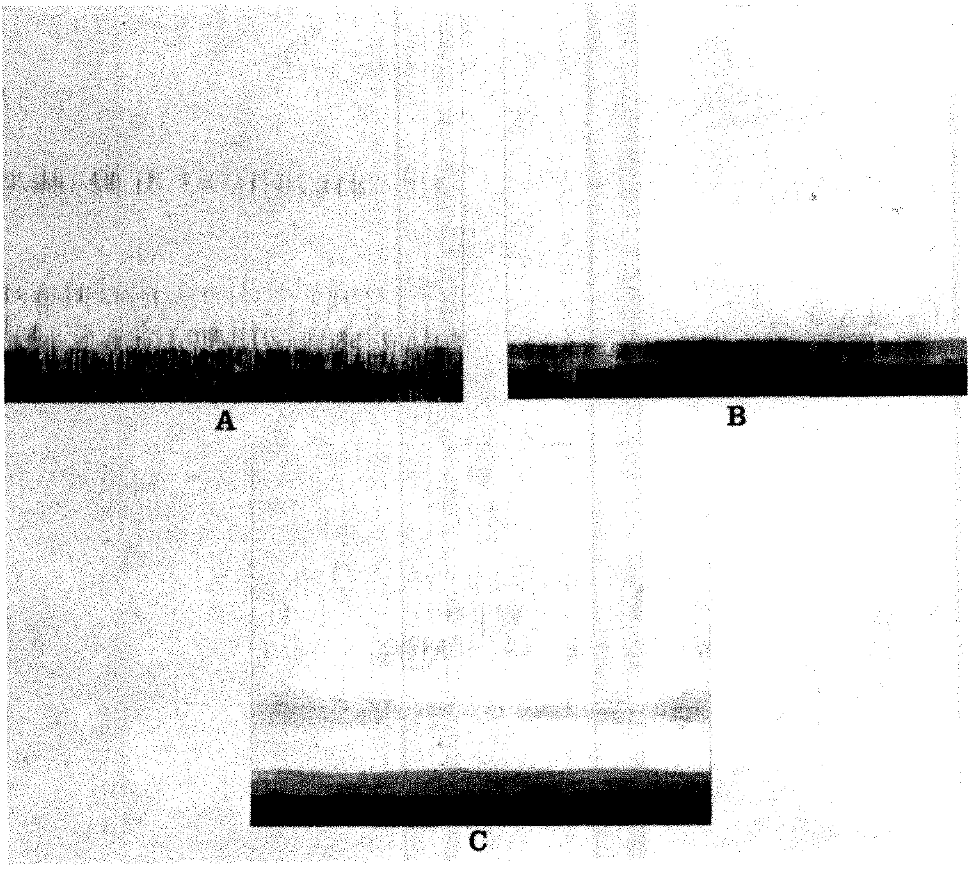

Fig. 3. (Case 1) Example of the spectrograms obtained in the TST. A) Preinjection. Note the aperiodicity of the vertical striations and the subsequent formant breakdown. B) Thirty seconds postinjection. The vertical striations have become regular and formants are becoming more defined. C) Finally, after pyridostigmine therapy a normal spectrogram is seen and there is even a suggestion of a tremulo in the voice.

pyridostigmine therapy with only minimal response. Previous electrophysiologic and pharmacologic testing was negative. Laryngeal examination was normal.

The preinjection spectrogram showed significant aperiodicity of vocal cord movement as evidenced by irregular vertical striations of the lower frequency regions. Mid and upper frequency breathiness was also observed. Thirty seconds after injection, a marked improvement in all aspects of phonation had occurred. The aperiodicity had nearly completely cleared with normal vibration of the vocal cord as represented by evenly spaced vertical striations along the baseline. Most of the excessive breathiness had also been eliminated. The spectrogram representing the patient's voice once placed on pyridostigmine showed even better periodicity of vocal cord movement. Excellent formant structure, resonance and overall strong voice with no dysphonic characteristics were observed.

Case 3 (C.O.). This 42-year-old female presented with a history of bilateral ptosis, generalized muscle fatigue and weakness, mild dysphagia and dysphonia. The patient's symptoms became more severe as the day progressed.

Neurologic evaluation showed definite ptosis bilaterally. Conjugate gaze was limited to 10° of movement in all directions. Laryngeal examination was

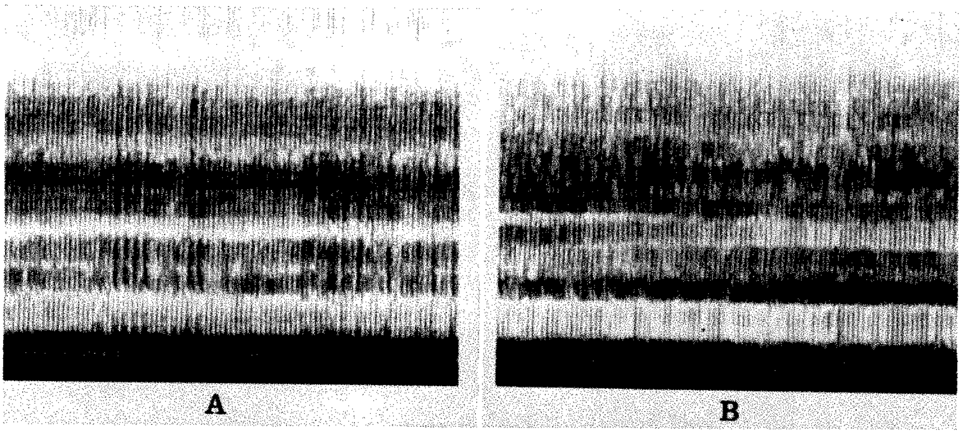

Fig. 4. (Case 4) Example of spectrograms, negative for myasthenia gravis. Note aperiodicity, breathiness and formant breakdown in both recordings. A) Preinjection; B) Postinjection.

normal. Electrophysiologic and pharmacologic examinations were unrewarding.

The preinjection voice spectrogram showed mid and high frequency energy, representing breathiness in the selected vowel sample. Apparently, incomplete vocal cord closure was occurring in spite of good periodicity of vocal cord movement. Thirty seconds postinjection, a significant amount of excessive breathiness had diminished. The spectrogram of the voice after pyridostigmine therapy was initiated, and again showed a strong, resonant vocal quality with excellent formant structure.

Case 4 (M.K.). This 69-year-old Caucasian female was seen with a chief complaint of hoarseness and loss of vocal power of three months duration. Her symptoms were inconsistent and not always present. A neurologic examination was unremarkable. Laryngeal examination showed no evidence of organic lesion. In view of her symptoms of progressive dysphonia, the patient was administered the TST (Fig. 4). The preinjection voice was relatively normal with slight traces of breathiness. Thirty seconds postinjection, no improvement occurred, in fact, there was a slight increase in the breathiness of the voice. In view of the lack of improvement in phonation with the TST, the examination was considered negative and a diagnosis of functional dysphonia was made.

Case 5 (J.W.). This 59-year-old Negro female was seen with complaints of hoarseness present for 1½ years. The hoarseness was sporadic in nature and she complained of progressive dysphonia with talking. No other neurologic symptoms were noted. Neurologic evaluation failed to reveal any distinct neurologic findings. A laryngeal examination was negative.

The patient underwent the TST and 30 seconds postinjection the voice had not changed appreciably. The postinjection spectrogram was judged to be essentially the same as the preinjection sample. The test was judged to be negative and a diagnosis of functional dysphonia was made.

Case 6 (A.R.). This 53-year-old Caucasian male presented with a dysphonia that worsened as the day progressed. There were no complaints of dysphagia, diplopia or generalized weakness. Neurologic evaluation was remarkable. Laryngeal evaluation showed bowed cords without anatomic lesion.

After edrophonium injection, the degree of aperiodicity of vocal cord movement was observed both pre-and post-injection. Excessive breathiness throughout the frequency spectrum was also observed. There was no significant improvement in phonatory function 30 seconds after the injection. The test was considered negative and a diagnosis of myasthenia laryngis was made.

DISCUSSION

By voice spectrographic analysis of a single, simple, prolonged vowel, the fundamental frequency of the voice can be analyzed for its periodicity (Fig. 1). This vocal characteristic is the acoustic end product of the regularity of compressions and rarefactions of air emitting from the larynx. The clarity of the formants can also be noted. These are the dark bands of the spectrographic tracing, indicating the overtones and resonance characteristics of the fundamental frequency (Fig. 1). Finally, the amount of breathiness as a measure of vocal cord approximation can be assessed. The breathiness is the middle and high frequency energy that is unrelated to distinct resonance and blurs definition of the formants (Fig. 1). All three of these features are simultaneously recorded on the spectrogram. The procedure is noninvasive, rapid and safe, and can be made from a high quality cassette recording. The sound spectrograph produces a permanent record with which to compare and refer.

This study demonstrates that in those patients with progressive dysphonia, the voice spectrogram can demonstrate the effects of edrophonium on the small muscles of the larynx. The spectrogram shows that the ability of the vocal cords to approximate with good muscle strength produces a dramatic improvement in the periodicity of the sound generated from the larynx following injection. Breathiness may be diminished and formant structure can be improved as the overtones are accentuated and become clearer. The improvement of breathiness and periodicity is strictly a laryngeal function.

The voice spectrogram can be utilized as an accurate assessment of the end point of the edrophonium test. It can be used to follow long-term treatment of dysphonia associated with myasthenia gravis.

The TST becomes an effective tool in distinguishing myasthenia gravis from other types of functional and neuromuscular dysfunctions of the larynx. Of special interest to laryngologists is the confusing nomenclature of myasthenia laryngis (case 6). This diagnosis, which encompasses bowed cords and progressive dysphonia in debilitated or elderly patients, is common. It is easily distinguished from true myasthenia gravis of the larynx by the absence of a positive TST. This test can also be useful in uncovering myasthenia gravis in patients with true organic lesions of the vocal cords. Polypoid laryngitis has been known to occur concomitantly with myasthenia gravis. This has an obvious importance in any persistent dysphonia following laryngeal surgery. Lastly, patients with functional dysphonia can be distinguished easily from myasthenia gravis by the test, as seen in this study (cases 4-6).

Patients with myasthenia gravis may present with progressive dysphonia as the sole manifestation of their disease. In such cases, standard electrophysiologic and pharmacologic testing of extralaryngeal musculature may be negative. Further, myasthenia gravis of the larynx may be far more common than would normally be expected in a clinical practice. The results of this study suggest that the TST is a new clinical investigative tool to establish the diagnosis of myasthenia gravis of the larynx.

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THE CASSELBERRY AWARD of the AMERICAN LARYNGOLOGICAL ASSOCIATION

The American Laryngological Association announces that it will receive essays or theses relating to the art and science of laryngology and rhinology for consideration of the Casselberry Award for 1978-79. The award is open to scientists, physicians, interns, residents and graduate students in laryngology and rhinology in the Americas. *For information write*: William M. Trible, MD, Secretary, American Laryngological Association, 110 Irving Street, N.W., Washington, DC 20010.

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GRAND ROUNDS — ALBANY MEDICAL CENTER
DIVISION OF OTOLARYNGOLOGY
JEROME C. GOLDSTEIN, MD, PROFESSOR AND HEAD

EPSTEIN-BARR VIRUS THE RAVAGER

SHARAD S. PARULEKAR, MS, FRCS
ARNOLD RAPOPORT, MD
DOMINICK F. PAONESSA, MD
JOSEPH KOUYOUMGIAN, MD

Dr. Sharad Parulekar: Chairman and colleagues, Epstein-Barr virus (EBV) is a large DNA virus belonging to the ubiquitous herpes group and is the most recently described of the four that infect man. It was first demonstrated by electron microscopy from Burkitt's lymphoma (BL) cell lines by Epstein et al.[1] In 1968, the Henles reported a positive seroconversion associated with EBV infection.[2] Epstein-Barr virus is a lymphotropic virus, its main target being the human B lymphocytes, which have specific receptors for it.[3] It establishes a persistent carrier state in the lymphoreticular system.[4] It plays the leading part in infectious mononucleosis (IM) and BL. Its association with nasopharyngeal carcinoma (NPC) is increasingly drawing attention. It possibly has some distant role in Hodgkin's disease, systemic lupus erythematosus, sarcoidosis and acute lymphatic leukemia.[5,6]

Viruses are intranuclear parasites. The viral genome invades and combines with the cell nucleus to take possession of the cell metabolism, to direct it to its own survival and propagation. The reaction of the cell is one of three types: 1) cell lysis, 2) symbiosis, or 3) tumor formation. To express it in another fashion; with a productive infection, there is viral replication and cell death; with a nonproductive infection, the viral genome may be either unexpressed in a symbiotic dormant stage, or be expressed in tumor formation. EBV infection is capable of exhibiting all these characteristics[7] (Fig. 1).

The virus is transmitted horizontally and enters the oropharynx to infect the tonsils primarily, as they are rich in B lymphocytes.[8] A lytic and persistent infection is produced and may be associated with recurrent episodes of tonsillitis.[8] The virus multiplies and enters the blood stream to set up a systemic infection of the B lymphocytes. Current evidence indicates that there is a mixed T lymphocyte response to the EBV infected ones, together producing a massive outpouring of atypical lymphocytes.[5] These specific killer T lymphocytes can lyse the infected ones, but the process is not complete. Part of the IM syndrome may reflect an acute rejection reaction of the lymphocytes.[5] The immunological events that turn IM on or off are not entirely clear, two thirds of those infected in the peripubertal years become afflicted with the classical clinical features; it is possible that the lymphocytes of young adults may be more mature. Further, heterophil antibodies may be induced in response to membrane induced changes of EBV, which perhaps is more fully expressed in the lymphocytes of young adults than those of earlier years.[5] Primary EBV infection in childhood and in a third of those individuals infected in later ages is possibly subclinical and expressed as a minor febrile illness associated with a mild pharyngotonsillitis, adenopathy and

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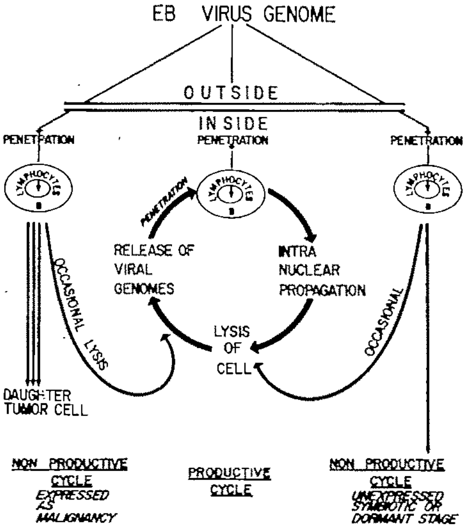

Fig. 1. Diagram to illustrate varieties of EBV infection in man.

serous otitis, and passes unnoticed. Heterophil antibodies and atypical lymphocytes are not always present.[9] Horowitz et al concluded that even the elderly are not immune and that mononucleosis should be included in the differential diagnosis of fever, sore throats or myaglia, with or without cervical lymphadenopathy occurring in the aged.[10]

Serology studies have shown there is a high maternally-derived antibody level in the infant which soon disappears, and the infant becomes seronegative. A gradual conversion to seropositive occurs, and the proportion of individuals converting increases with age as more and more individuals become infected. In late adolescence 80% of the population become permanently seroconverted. If the world incidence of EBV infection were divided into age groups, then in congested, overpopulated or underprivileged societies, there is early seroconversion in the 2 to 7-year olds suggesting a primary wave of infection. In higher socioeconomic groups, particularly in Western societies a secondary wave of infection occurs in late puberty, probably because of the prevalence of kissing.[4,7,9] Exuberance increases the chance of infection: the more the variety, frequency and ardor of osculation, the greater is the mucosal contact and salivary exchange. Niederman et al[11] hypothesized that the low transmissibility of mononucleosis is due to cellular kissing, i.e., a free exchange of EBV infected cells and concluded that the persistence of the oropharyngeal virus for months appeared to be due to the presence of the agent in the saliva, rather than just in the posterior pharynx and tonsils. They persistently demonstrated the virus in Stensen's duct.[11]

In 1889, Pfeiffer described for the first time the clinical features of "glandular fever."[12] Sprunt and Evans in 1920 described the characteristic mononuclear leukocytosis and coined the term infectious mononucleosis.[13]

After an incubation period of about 5 to 12 days, IM is manifested by a sudden generalized weakness, malaise, anorexia, headache, and a persistent fever. The sore throat is troublesome. The pharyngeal mucosa and palate swell and there is massive hypertrophy of Waldeyer's ring. The tonsils have a characteristic appearance.[14] The cervical and other nodes including axillary, epitrochlear, inguinal, mediastinal and mesenteric are tender and enlarged. Splenomegaly occurs. There is a generalized erythematous or maculopapular eruption and the patient may be jaundiced. Hoagland, cited by McCurdy, differentiated the symptoms into two categories of presentation; 1) pharyngeal syndrome (80%) and 2) typhoidal syndrome (20%).[15] The disease is thought to be self-limited with a variable duration of about one to two weeks. The patient, during the height of the infection, exhibits characteristic hematological and serological findings.[14] The anti-EBV antibodies, which appear in the first two weeks of onset, remain high during convalescence, and persist for several years, possibly for life.[16]

The respiratory complications of mononucleosis may be of three types; 1) obstructive adenotonsillar hypertrophy, 2) obstructive pharyngolaryngeal edema, or 3) neurological respiratory paralysis. This could lead to dysphagia, and this combining with the accompanying anorexia and toxemia, may result in a significant weight loss and dehydration. Epistaxis, stomatitis, serous otitis and mastoiditis occur. A characteristic reversible ampicillin rash has been described to be so frequent as to be diagnostic.[14] Streptococcal pharyngotonsillitis has been described in 30% of cases.[15] To the best of our knowledge, peritonsillar inflammation or abscess has not been previously described as a complication of IM. We had two interesting cases. The neurological complications are many and varied. Gautier-Smith classified them into lymphocytic meningitis; encephalomyelitis; mononeuritis; and polyneuritis.[17] Several cases of Guillain-Barré syndrome have been described. Cranial nerve involvement is relatively uncommon, but mononeuritis of all the cranial nerves has been described. Anosmia, III, IV and VI cranial nerve palsies have been described.[18] Dysfunction of cranial nerves V and VIII to XI has been reported.[18] Hypoglossal nerve involvement both isolated and as a polyneuritis variant involving cranial nerves IX to XI has been noted.[19] Of special otolaryngologic interest are facial palsy and paresthesia of the face, sensorineural hearing loss and episodic vertigo.[14] Periorbital edema,[15] conjunctivitis, uveitis, optic neuritis, retinal hemorrhage, splenic rupture, pneumonitis, pericarditis and hemolytic anemia are other possibilities.[20] The estimated mortality rate is as high as one per 3000 cases: the most common cause of death is splenic rupture, followed by neurological complications.[15] Deaths due to profuse nasopharyngeal hemorrhage and laryngeal edema have also occurred.[15]

There is no specific therapy and treatment is usually symptomatic. Formerly, arsenicals were considered useful. This cure or kill treatment was, late in 1955, replaced by steroids which proved beneficial in IM of any degree of severity.[20] Sometime around this period, adenotonsillectomy seems to have been practiced in Europe for the pharyngeal type of disease.[20] Opinion against tonsillectomy has prevailed and the attributed reasons are 1) generalized toxemia, 2) difficult anesthesia, 3) risks of undermining resistance and spreading infection, and 4) postoperative bleeding. The common use of antibiotics against secondary infection, intravenous fluid hydration, and nutrition as well as use of diathermy cauterization, seem to be the answers to the above theoretical factors. Awake intubation,[21] or local anesthesia may possibly be the answer to the anesthesia risk.

The line of management, at the present time, seems to be steroid and antibiotic therapy in the initial stages, and if respiratory embarrassment increases, tonsillectomy would seem to be useful.[14,20] The advocates for this procedure believe that it is safe, and perhaps should be practiced more often as it may shorten the period of suffering for the patient.[20,22,23] Tracheostomy is indicated when the patient is very toxic, has pharyngolaryngeal edema, or is in respiratory paralysis and needs management on a respirator.

The ravages of EBV do not stop with IM and its complications. The etiologic trails of BL and NPC are getting hotter and hotter and as Evans[5] puts it, the web is gradually closing around EBV. IM confuses and confounds the clinician in his diagnosis of acute lymphatic leukemia and may perhaps play an immunosuppresive role, thereby switching on the leukemic process.[6]

BL is prevalent in certain African malarious areas. Burkitt propounded that the essential multifocal nature of the African tumor suggested a widespread infection of the lymphoreticular system; whereas the discrete tumor deposits, the rarity of leukemia, and the remarkable occurrence of long-term survivors, irrespective of the regularity or intensity of therapy all pointed to a containment by the hyperimmune response to malaria. The antigenicity, tumor specificity and space-time clustering exhibited by BL strongly suggest EBV in a causal role.[24] Seroepidemiology has shown very high antibody titers to EBV in BL and both the squamous and lymphoepitheliomatous types of NPC, and this is not shown by any other tumor in the body.[25] In NPC, the exclusive and regular presence of the viral genome in a distinctive tumor, irrespective of origin or endemicity, makes the association strongly suspicious of an etiologic role, although at this juncture, it is impossible to go for or against a causative versus a promoting influence. It would not be surprising if a cooperative interplay of viral transformation and host cell genetics eventually emerges, as NPC is very common in the Chinese.[3,25,26]

Permanently growing, continuous, "immortalized" lymphoblastoid lines have been grown from biopsy specimens of BL and NPC, or the blood of clinical or subclinical IM or even healthy donors if somehow contaminated with EBV. The fact emerged that immortalization occurs in only seropositive individuals or seronegative ones on contamination, indicating the absolute need of EBV genetic information. With BL it is the malignant cells that grow out. In NPC, IM or healthy individuals, the in vivo lymphoid cells are nonmalignant. When grown in vitro however, all these lines appear similar, assume malignant characteristics and on heterotransplantation to laboratory animals lead to highly malignant fatal tumors, sometimes even without immunosuppression.[7]

The story of EBV has just begun. The supporting proofs are almost conclusive for its role in IM and BL and proof connecting it to NPC is quickly accumulating. Like any novelty, it has been blamed for other diseases. The question whether EBV is an innocent passenger virus or an etiological agent of human oncogenesis continues to perplex scientific minds. The possibility always remains that IM is not as benign and self-limiting as clinicians would like to believe. The virus may lurk in the darkness and in view of the complexities of the human body it may set up a malignant process if it is given the opportunity.

I have two interesting cases to present to you. Our first case was that of L.B., a healthy young adult male who came to the emergency room on September 22, 1977 complaining of a severe sore throat and fever. A Monospot® test was positive. IM was diagnosed, the patient was put on symptomatic treatment and sent home. He returned two days later with severe respiratory distress and dysphagia and was admitted. He had a maculopapular rash, enlarged spleen and massive lymphadenopathy of the neck. The tonsils were beefy red with a grayish exudate and they met in the midline. The Monospot® test was repeatedly positive and the blood showed absolute lymphocytosis and high atypical lymphocyte counts (30-50%). The patient mentioned prior episodes of tonsillitis. He was started on intravenous fluids and intravenous aqueous penicillin two million units every four hours and Solu-Cortef® 100 mg every six hours. The toxicity and symptoms worsened; the temperature stayed high at around 38.9 C rectally. The respiratory distress increased. At this juncture only a narrow chink was left for pharyngeal air transfer and for the first time there was significant palatal edema and left peritonsillar bulging. A lateral x-ray of the neck showed marked swelling of the soft tissues in the hypopharyngeal region with almost complete supraglottic obstruction. There were bubble type lucencies in the density and the retropharyngeal

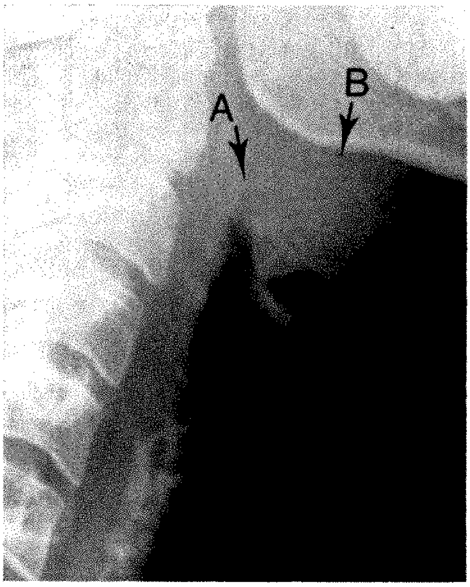

Fig. 2. (Case 1) Lateral x-ray of the neck demonstrating (A) supraglottic airway obstruction and (B) bubble type lucencies in area.

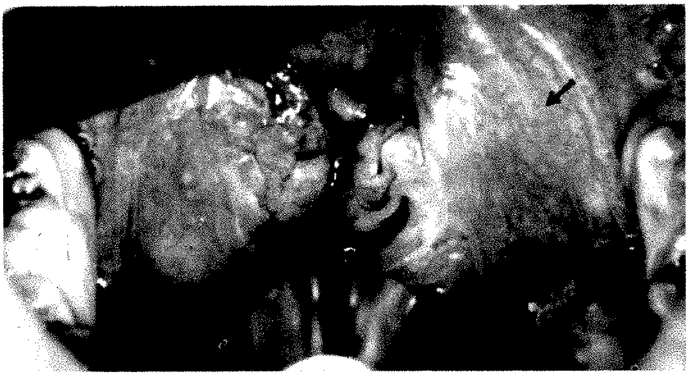

Fig. 3. (Case 1) Photograph of the oropharynx on Oct. 7, 1977, the day of tonsillectomy, showing left peritonsillar swelling (arrow) and total closure of the oropharyngeal isthmus.

tissues were prominent (Fig. 2). There was never any trismus. After much pondering, a difficult tracheostomy was done under local anesthesia on September 30, a week after admission.

A left peritonsillar incision was made and it drained about 10 cc of pus. The airway distress was relieved but the temperature stayed around 38.9 C for about 36 hours. Repeated dilatation of the peritonsillar incision allowed about 10 cc pus to be drained on two occasions. The culture report was Gram negative bacilli and diplococci and Gram positive cocci, predominating anaerobic bacteroides. The antibiotic therapy was changed to intravenous gentamicin 60 mg every eight hours and intravenous clindamycin 600 mg every six hours. A gradual lowering of the temperature followed. The tonsils were still massive; the sore throat, dysphagia, toxemia and seepage of pus from the incised area still continued; hence a week after the first operative procedure, a tonsillectomy was done (Fig. 3). Thereafter, the patient showed a rapid recovery; swallowing was possible in 24 hours; he was extubated in 48 hours and discharged a week later. He is under regular observation. Histology of the tonsils showed only chronic inflammation.

Our second case was that of an 18-year-old healthy male who came to the emergency room with a history of sore throat for a week which had worsened on that day. He was sent home on oral penicillin. He developed high fever and trismus, and was admitted the next day. The patient did not at any time have significant dysphagia or respiratory distress. The Monospot® test was positive and absolute lymphocytosis and high atypical lymphocyte counts were present. IM and quinsy were diagnosed. The patient was started on intravenous fluids and intravenous aqueous penicillin 1.2 million units every four hours. The left peritonsillar abscess was incised and drained with improvement in symptoms. The fever gradually came down and the patient was discharged home four days later on oral penicillin. He was followed regularly in the otolaryngology clinic. Tonsillectomy was offered, but the patient declined.

Dr. Dominick Paonessa: Mr. L.B., the first patient, was first seen in my office on September 24, 1977 and appeared quite sick with findings as described by Dr. Parulekar. I admitted him to St. Peter's Hospital and he was started on the usual conservative therapy and his subsequent course proved very interesting and instructive. The simultaneous occurance of IM and quinsy was unusual. By pure coincidence, Dr. Kouvoumgian had another case three months earlier, who responded to conservative therapy and incision and drainage of the abscess. Our patient, however, did not respond to medical therapy and became increasingly dyspneic. We felt tonsillectomy might be the answer, but hesitated because of the anesthesia risk. Local anesthesia may have been helpful, but we decided that it would be far safer to do a tracheostomy. The respiratory problem was relieved, but the patient was still in discomfort. Dr. Rapoport attended the patient during my absence and did the tonsillectomy with complete relief to the patient. The absence of trismus was significant and this was probably due to the masking of inflammation by steroid therapy. The emergence of penicillin-resistant bacteroides was notable and response to change of antibiotic therapy and tonsillectomy was remarkable.

Dr. Jerome Goldstein: There is one more important observation about EBV I would like to bring to your notice. When following a patient with NPC, EBV titers give an indication of the response of the NPC to the treatment offered, and in fact the titers are useful in the long-term follow-up of the patient. A lowering of the titer indicates a good response, whereas, in the later months if the titer goes up, it indicates metastatic or recurrent disease.

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EDWIN NASH BROYLES, MD

1894-1977

Edwin Nash Broyles, an Honorary Fellow of the American Laryngological Association and an Honorary Member of the American Broncho-Esophagological Association, died November 11, 1977. He was elected to fellowship in 1940 and served as counselor, librarian, historian and editor (1955-1960), vice president in 1952 and president (1960-1961) of the American Laryngological Association. Dr. Broyles received the Newcomb Award in 1965. He was elected to membership in the American Broncho-Esophagological Association in 1936, served as vice president in 1947, secretary (1948-1953) and president in 1953. He was the Guest of Honor of this association in 1962 and received the Chevalier Jackson Award in 1963.

A native of Atlanta, Ed Broyles graduated from the Johns Hopkins Medical School in 1919 and finished his residency in Otolaryngology at the Johns Hopkins Hospital in 1922. With the exception of four years in the Pacific as captain in the Medical Corps of the Navy, Dr. Broyles was in charge of the endoscopic clinic of the Johns Hopkins Hospital for four decades from 1923. In 1963, the newly renovated endoscopic clinic at Johns Hopkins was dedicated and named for him.

In the thirties, Dr. Broyles worked with his life-long friend, William Reinhoff, in the development of pneumonectomy and with his Professor, Samuel Crowe, in the development of laryngectomy. Broyles' pioneering application of whole organ serial horizontal sectioning techniques to the study of the anterior commissure tendon is a milestone in the application of basic laboratory methodology to the problem of laryngeal cancer. As an innovator, Dr. Broyles improved many instruments; most notably, his development of a series of bronchoscopic telescopes and a family of bronchoscopes to accommodate them. Similarly, he devised an optical nasopharyngoscope. In 1962, his address as Guest of Honor of the American Broncho-Esophagological Association pointed the future of fiber illumination.

As the many medical student residents who were welcomed into Dr. Broyles' home can testify, any history of his attributes as clinician, teacher, innovator and researcher is incomplete if it fails to mention the pervasive warmth of his personality. A truly gentle man he was the focus of a generation of Hopkins residents who were his "boys." Beyond the Hopkins, laryngology, and medicine, he was loved and respected within the Baltimore community where he was president of the Maryland Club from 1961 to 1964.

Dr. Broyles will long be remembered as a pioneer laryngologist and broncho-esophagologist.

Gabriel F. Tucker, Jr., MD

COMMUNICATIONS

Dear Editor:

The Task Force from the Symposium on Impedance Screening for Children (Nashville, 1977), exerted an enormous amount of time, effort and energy in their formation of recommendations for impedance screening.[1] However, consensus was not reached on all issues and we believe that the final recommendations clearly demonstrated the old adage that ". . . a camel is the result of a committee trying to design a horse." We do recognize that the final product represents many vested interests from several professional points of view concerning impedance screening and ear disease. It is our intent in this letter to express viewpoints of some members of the Task Force which were not included in, or are at odds with, the final set of "Recommendations from the Task Force."

First, and foremost, we oppose the Task Force statement that "At the present time, and until additional information has been developed, the Task Force does *not* recommend the use of impedance measurements for universal (mass) screening on a routine basis for the detection of middle ear disorders in children of any age group." This statement becomes a blatant contradiction when one considers that the Task Force report also states that middle ear effusions are a prevalent condition among infants and children, and that evidence exists that "early treatment may be of advantage in preventing certain unfavorable long-term developmental consequences in some children - - -." Clearly, the recommendations are phrased in such a way as to act as a deterrent to the early identification and management of this prevalent disease. It is incongruous that a set of referral criteria and other guidelines for impedance screening are presented by the Task Force, but at the same time identification by impedance screening is explicitly discouraged. It is our contention that this position has been taken, not because the impedance screening procedure lacks validity, but because there is considerable uncertainty about medical management of the identified pathologic condition.

We understand and acknowledge that middle ear effusions are frequently transient and self-resolving, a situation which has contributed to overreferral in screening programs. However, at the same time we are of the opinion that sufficient information presently exists to formulate specific referral criteria which would consequently make it viable to utilize impedance screening as a public health measure. While we did not urge the Task Force to advocate impedance screening as an *essential* screening procedure, we believe it is a reasonable procedure given the appropriate guidelines and referral criteria.

We do acknowledge the fact that additional research is needed before mass impedance screening can be advocated. Much of the data which was considered by the Task Force was obtained "clinically" rather than in screening programs and was, therefore, not truly representative of the population of children for whom screening measures are intended. In addition, the radical change in impedance instrumentation during the last several years promises to result in even more effective screening, but this has yet to be established. Nevertheless, at the same time, we support, rather than discourage, the use of impedance screening as a means of increasing the wealth of information which would be generated only through a variety of screening programs.

We also fault the recommendations because there is no category for initial screening failure and referral. The recommendations state that ". . . any child failing the initial (impedance) screening should be retested in four to six weeks." We support the concept of monitoring or retesting as an essential component which will minimize overreferrals in impedance screening programs. However, we do not agree that a child with a "nonmobile" TM or "flat" tympanogram, with an absent acoustic reflex on the initial screen should await a period of four to six weeks before a repeat test confirms the presence of pathology. Such findings on initial screen should be cause for immediate referral and medical evaluation. They also should be the cause for implementing more careful hearing testing and appropriate educational considerations.

In summary, we recognize the need for impedance screening guidelines, and the Nashville Symposium certainly provided the appropriate impetus for Task Force discussions. However, we feel that the final recommendations did not reflect the consensus of the Symposium participants. We hope our few words will kindle rethinking of these issues.

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Jerry L. Northern, PhD, Denver, CO
Joanne Rosenberg, MA, Philadelphia, PA
Laura Wilber, PhD, Evanston, IL
Virgil M. Howie, MD, Huntsville, AL

Dear Editor:

In objecting to the Task Force recommendations which advised against mass impedance screening at the present time, Dr. Feldman and his cosignatories appear to have missed the essential points. True, the Task Force report acknowledged the possibility that "early treatment may be of advantage in preventing certain unfavorable long-term developmental consequences in some children," but in the same sentence the report went on to say "but the evidence for this is not conclusive and more studies are necessary to confirm this possibility." True also that the Task Force recommendation was based in part on the fact that "there is considerable uncertainty about medical management" of middle ear effusion, but the key point to be appreciated is that in many instances there is uncertainty whether intervention of *any* kind is warranted.

We thus have a disease state — otitis media with effusion — that in most instances may resolve spontaneously; that may have no lasting ill effects; and for which specific treatment may often, if not usually, be inadvisable. Under the circumstances, mass screening programs would stand a good chance of promoting large-scale over-referral and over-treatment, much of the latter inevitably surgical.

We disagree with Dr. Feldman et al that the information we need "would be generated only through a variety of screening programs." The information we need most involves the natural history, treatment outcomes, and long-term consequences of otitis media with effusion. The way to improve our understanding of impedance screening itself is to undertake carefully planned studies of screening under controlled conditions, not to launch willy-nilly into a variety of community programs of inconsistent design, whose uncharted results will necessarily defy evaluation.

It remains to be shown whether impedance screening programs will produce more good than harm. We favor efforts designed to test this question, but we oppose programs that assume incorrectly that the question has been already answered.

In screening programs already embarked upon, whether the child with a "flat tympanogram" should receive "immediate referral and medical evaluation" depends in large degree on the resources available. Not every community in which impedance screening is possible contains, in addition, physicians skilled in the diagnosis and management — or judicious non-management — of otitis media with effusion. Keeping in mind that screening is for the purpose of identifying asymptomatic subjects in nonclinical settings, it seems unlikely that asymptomatic children with flat tympanograms will be harmed by a waiting period of four to six weeks in order to be certain that the condition has not resolved spontaneously. The Task Force was careful to recommend that adequate notification be provided the parents or guardians of such children.

For a more complete discussion of the question of impedance screening the interested reader is directed to the full proceedings of the symposium published by Grune & Stratton, Inc. in July 1978 under the title *Impedance Screening for Middle Ear Disease in Children*.

Impedance testing is a marvelous tool; let's be certain that we use it to children's advantage rather than their detriment.

Sincerely yours,

Jack L. Paradise, MD
Charles D. Bluestone, M.D.
Fred H. Bess, PhD
Don A. Harrington, PhD
Jerome O. Klein, MD
Earl R. Harford, PhD
Samuel R. Bashore, MA
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BOOK REVIEWS

Scientific Foundations of Otolaryngology

Edited by *Ronald Hinchcliffe* and *Donald Harrison*. Hard cover, black and white illustrations, referenced, indexed, 976 pp, 1976. William Heinemann Medical Books publication, distributed by Year Book Medical Publishers, Chicago. Price: $59.95

This unique book, edited by two of England's outstanding members of our specialty, is a compilation of scientific and clinical information which is of particular importance to the student, the physician in training, the teacher, and the investigator.

The book contains a wealth of information which is not readily available, with emphasis upon mathematics, chemistry and physics; provides many short essays in highly specialized aspects of the ear, nose and throat and related specialties; encompasses history, art, and the law, and even provides a short multilingual dictionary. The volume is well-illustrated with line drawings and half-tones and there has been no limitation in the allocation of space for comprehensive tables. Since each special essay, of necessity, had to have some limitations as to length, excellent bibliographies are provided with each section.

The contributing authors consist of clinically and scientifically oriented investigators and practitioners in the expanded otorhinolaryngology specialty, who appear to be fully aware of the sophisticated research and clinical and surgical techniques to which the young trainee is exposed. These authors are alert to the confusion of terminology which plagues the author and editor and have dealt with it forcefully and conclusively. For those who struggle with acquiring information on proper terminology, international units, etc., an appendix for this purpose is available.

This book should be in every medical school library and in all departmental libraries utilized by clinical and research otolaryngologists, audiologists, speech pathologists and neurotologists.

Ben H. Senturia, MD
St. Louis, MO

Cleft Palate: Middle Ear Disease and Hearing Loss

Edited by *Malcolm D. Graham*. Hard cover, black and white and color illustrations, referenced, indexed, 131 pp, 1978. Charles C. Thomas, Springfield, IL. Price $15.00

This new monograph provides a clear and concise updating of the information available on the otologic aspects of cleft palate deformities. The book begins with a consideration of the anatomy and physiology of the cleft palate, Subsequent chapters consider eustachian tube anatomy and physiology, prevalence and pathogenesis of ear disease, the relationship of pharyngeal disease to ear disease, and the anatomy and pathology of the tympanic membrane in the middle ear. The chapters on therapy focus on the otologic management, the handling of communication problems in the child with cleft lip and cleft palate, and treatment of language learning disorders.

The chapters are clearly written by the various authors and are accompanied by appropriate line-drawings, charts, graphs and colored illustrations. Most chapters include extensive bibliographic references for further consultation.

This book stresses the need for a multidisciplinary approach to the evaluation and treatment of patients with otologic abnormalities associated with cleft palate deformities. Hopefully, it will be of use to otolaryngologic practitioners and residents, as well as to audiologists, speech pathologists and other members of the therapeutic team.

Frank E. Lucente, MD
Elmhurst, NY

Cryosurgical Advances in Dermatology and Tumors of the Head and Neck

Edited by *S. A. Zacarian*. Hard cover, color and black and white illustrations, indexed, 272 pp, 1977. Charles C. Thomas, Springfield, IL. Price $33.00

This book is edited by a dermatologist with wide experience in the treatment of cancer of the skin, specifically in the areas of cryogenics, cryobiology, cryonecrosis and all other aspects involving the application of subzero temperatures in living systems.

This is a book of 272 pages and 11 chapters. It is well illustrated with many black and white and colored photographs. However, only two chapters in the book are of specific interest to the head and neck surgeon interested in adapting or utilizing cryosurgery for his patients. In one of these, Andrew A. Gage describes his techniques of treatment and results for cancer of the oral cavity. In another chapter, Daniel Miller discusses his methods in the use of cryosurgery for various benign and malignant neoplasms of the head and neck. He also includes a discussion of the treatment of papillomas of the larynx and Tl glottic carcinoma. The last chapter deals with cryoimmunology and is largely speculative.

For those interested in cryosurgery and its possible application to diseases of the head and neck, the book will serve as a good reference volume.

James R. Chandler, MD
Miami, FL

Psychophysics and Physiology of Hearing

Edited by *E. F. Evans* and *J. P. Wilson*. Hard cover, black and white illustrations, indexed, 525 pp, 1977. Academic Press, London. Price: $27.35

These collected papers are from an international symposium sponsored by The Royal Society, The Wellcome Trust and Amplaid, held at the University of Keele April 12-16, 1977. The contributors are the leading contemporaries in their fields of endeavor.

The book is divided into sections covering cochlear mechanisms, frequency selectivity, pitch perception, temporal factors in hearing, and finally, binaural and central processing.

Some of the highlights are: an excellent discussion of sensory hairs in the ear by Flock. (Reported here probably for the first time is the discovery of an actin core in the stereocilia. Does this mean that stereocilia can retract?); EM studies of the innervation of the hair cell by Bredberg and others too numerous to mention.

Rhode presents his classical observations on the mechanics of two tone interaction, utilizing the Mossbauer effect to directly observe basal membrane motion. He concludes that two tone suppression can occur purely as a mechanical effect. The discussers of Rhode's paper argue that combination tones (i.e., intraaural harmonics) are not normally heard; in fact, Goldstein doubts their presence as mechanics correlates at these levels of stimulation.

Greenwood presents his excellent data on basilar membrane travel time function which now and for the foreseeable future will be used as standards of reference.

The introduction describes the so-called "second or neural filter." The mechanism of this important function appears to be no better understood than when von Békésy first hypothesized "neural sharpening" to explain the sharpness of frequency discrimination.

One wonders in all of this material why there are no reports of investigation of the function of the cochlear efferent systems. Neural feedback mechanisms described long ago by Sherrington for the motor systems, may also have an important role in sensory mechanisms.

This work contains a large amount of data which no doubt will serve as excellent reference material for the serious student. It is, however, a bit too technical for the casual reader.

Robin P. Michelson, MD
Redwood City, CA

ABSTRACTS FROM NATIONAL AND INTERNATIONAL JOURNALS

Removal of Foreign Bodies (Two Teeth) by Fiberoptic Bronchoscopy

Fieselmann JF, Zavala DC, Keim LW: Chest 72:241-243, 1977

With increasing experience with fiberoptic bronchoscopy and the addition of the claw, basket forceps, and balloon catheter, the flexible fiberoptic bronchoscope has become a very useful adjunct to the rigid bronchoscope for foreign body removal. It is particularly advantageous for peripherally located objects that in the past required thoracotomy and transpleural bronchotomy. It is also especially useful in patients being mechanically ventilated or in those with fractures of the jaw, cervical spine or skull. A 76-year-old male who aspirated two teeth and sustained a fracture of the skull and jaw is presented. He had the foreign bodies removed from the right lower lobe using fiberoptic bronchoscopy with a wire basket and Fogarty® balloon catheter.

A. Blitzer

A New Histochemical and Biochemical Approach to Olfactory Esthesioneuroma

Micheau C: Cancer 40:314-318, 1977

Six cases of olfactory esthesioneuroma were studied using electron microscopy and histochemical and biochemical tests in an attempt to clarify the site of origin of this rare tumor. Electron microscopy revealed electron dense, membrane-bound granules generally regarded as the storage sites of biogenic amines. Olfactory esthesioneuroma and neuroblastoma had similar activity when tested for dehydrogenase, MAO, nonspecific esterases, chloresterases, alkaline and acid phosphatases, and aminopeptidases. Immunohistochemical tests for dopamine beta hydroxylase were positive in all six cases of olfactory esthesioneuroma. The fluorescence was localized to the cytoplasm as has been described in neuroblastoma. The biochemical assay for dopamine beta hydroxylase in the sera of patients with olfactory esthesioneuroma was found to be lower than in patients with neuroblastoma. The olfactory esthesioneuroma appears to be similar to the neuroblastoma on a structural and biochemical basis.

A. Blitzer

Effect of Cobalt-60 Radiation on the Pulp of Restored Teeth

Nickens GE, Patterson SS, El-Kafrawy AH, et al: J Am Dent Assoc 94:701-704, 1977

The dental pulps of two young adult *Macaca speciosa* monkeys (a male and a female) were studied. Both had the same metallic and composite resin restorations placed in identical teeth. One received a total of 7,600 rads delivered via a 60 Co Eldorado unit to the midline according to techniques employed at the Indiana University Hospital. Both animals were sacrificed four months after irradiation had been completed on the one monkey. Pulpal findings were the same on both animals. Damage to the surrounding tissue in the irradiated animal where the metallic fillings were placed seems to corroborate the findings of Bettke and others in their paper when metallic restorations had been left in place in areas of the mouth subject to irradiation.

J. D. Piro

The Role of the Prosthodontist in Secondary Management of Facial Trauma

Moore DJ: J Prosthet Dent 38:441-445, 1977

Trauma to the face and jaws can occur from gunshot wounds, motor vehicle accidents, sports injuries, burns, and industrial accidents. A team approach to these problems is proposed. Prosthetic rehabilitation of patients afflicted with major trauma to the midface and interoral structures via accidents begins with the surgery. This initial start by the surgical team often assisted by the prosthodontist will then be followed by secondary rehabilitative procedures. These will be either prosthetic or surgical or a combination of both. Prosthetic treatment will often be protracted and complicated (especially in its technical aspects) and this must be understood by the surgical and other members of the team. The article is limited to the intraoral aspects of rehabilitation. Treatment should begin with correct alignment of osseous structures followed by resolution of the soft tissue components. Various techniques and devices to accomplish the resolution of these injuries are listed. The importance of the transitional prosthesis is emphasized. The author states that the prosthodontist should strive for simplicity in the fabrication of the definitive prosthesis. An excellent bibliography covering both intraoral and extraoral aspects of facial trauma is given.

J. D. Piro

A Human Syndrome Caused by Immotile Cilia

Afzelius B: Science 11:317-319, 1976

Cilia function as a major respiratory clearance mechanism and are essential for gamete motility in both males and females. This paper presents four patients with immotile spermatozoa. Three of these also gave histories of chronic sinusitis, bronchitis, recurrent pneumonia, frequent "colds" and ear infections. This clinical presentation is consistent with a defect in ciliary function. All patients demonstrated decreased clearance of radiolabelled aerosols from the lungs with suppression of cough. Electron microscopy of spermatozoa cilia revealed an absence of dynein arm crosslinks between microtubules. This is postulated to be the fundamental genetic defect responsible for the syndrome complex. Situs inversus totalis was noted in three of these patients for which various pathophysiologies related to microtubular movement were advanced.

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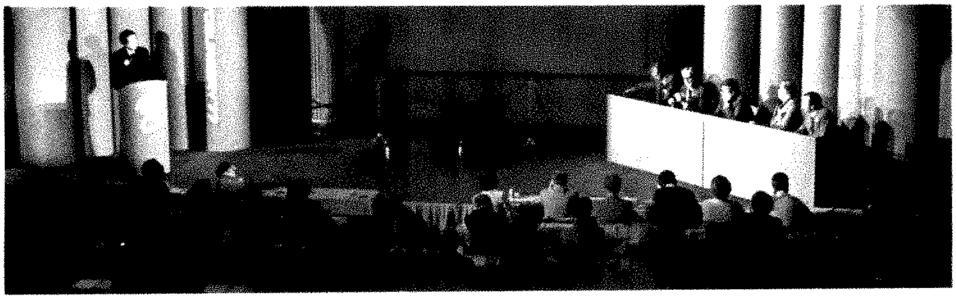

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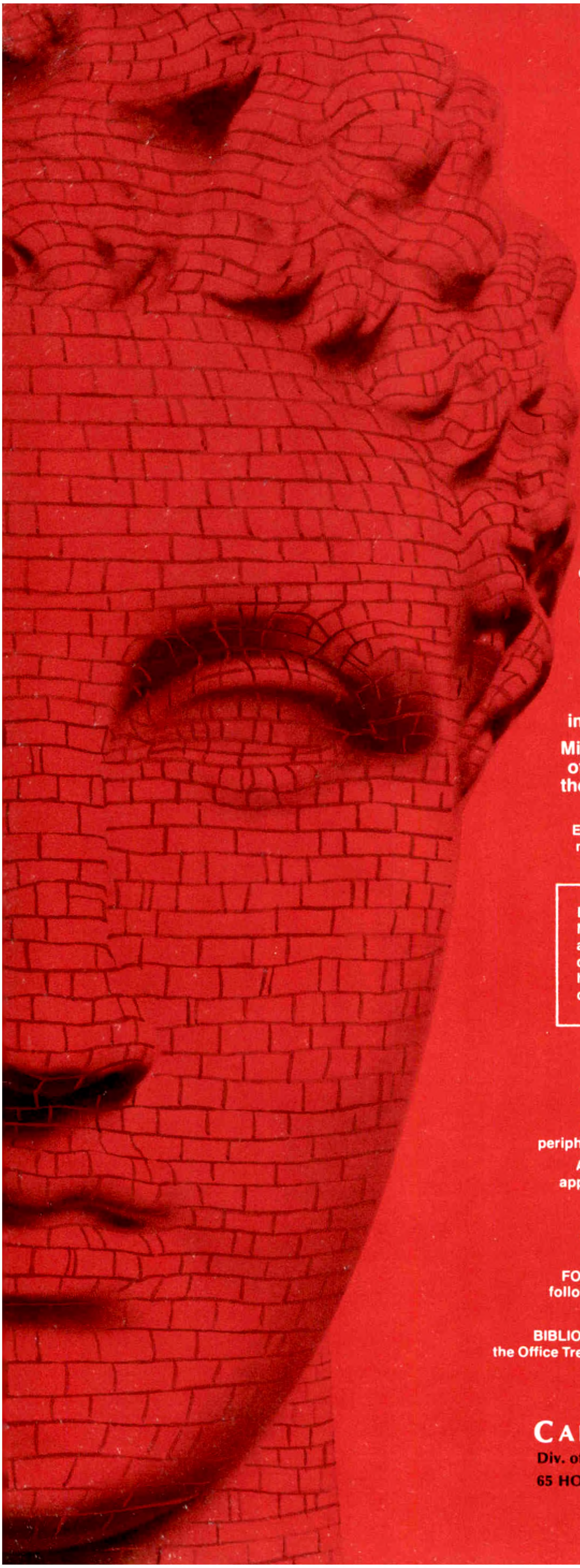

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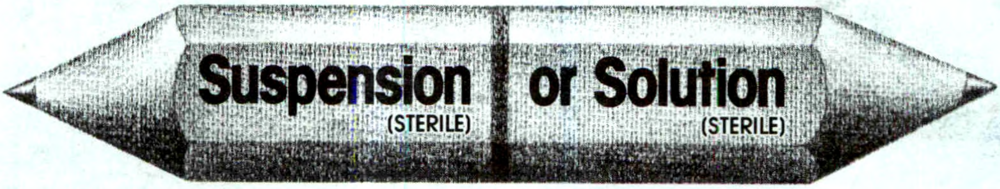

INDICATIONS:
For the treatment of superficial bacterial infections of the external auditory canal caused by organisms susceptible to the action of the antibiotics, and for the treatment of infections of mastoidectomy and fenestration cavities caused by organisms susceptible to the antibiotics.

DESCRIPTION:
Each cc contains: Aerosporin® brand
Polymyxin B Sulfate .... 10,000 units
Neomycin Sulfate .... 5 mg
(equivalent to 3.5 mg neomycin base)
Hydrocortisone .... 10 mg (1%)
The vehicle contains the inactive ingredients cetyl alcohol, propylene glycol, polysorbate 80, purified water and thimerosal (preservative) 0.01%.

PRECAUTIONS:
This drug should be used with care in cases of perforated eardrum and in long-standing cases of chronic otitis media because of the possibility of ototoxicity caused by neomycin.

ADVERSE REACTIONS:
Neomycin is a not uncommon cutaneous sensitizer. There are articles in the current literature that indicate an increase in the prevalence of persons sensitive to neomycin.

BENEFITS:
Indications include infections of mastoidectomy and fenestration cavities caused by organisms susceptible to the antibiotics.

INDICATIONS:
For the treatment of superficial bacterial infections of the external auditory canal caused by organisms susceptible to the action of the antibiotics.

DESCRIPTION:
Each cc contains: Aerosporin® brand
Polymyxin B Sulfate .... 10,000 units
Neomycin Sulfate .... 5 mg
(equivalent to 3.5 mg neomycin base)
Hydrocortisone .... 10 mg (1%)
The vehicle contains the inactive ingredients glycerin, hydrochloric acid, propylene glycol, purified water and potassium metabisulfite (preservative) 0.1%.

PRECAUTIONS:
This drug should be used with care when the integrity of the tympanic membrane is in question because of the possibility of ototoxicity caused by neomycin.

ADVERSE REACTIONS:
Neomycin is a not uncommon cutaneous sensitizer. There are articles in the current literature that indicate an increase in the prevalence of persons sensitive to neomycin. Stinging and burning have been reported when this drug has gained access to the middle ear.

BENEFITS:
Clear visualization of field. Does not have to be shaken.

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS COMMON TO BOTH PRODUCTS:
CONTRAINDICATIONS:
In individuals who have shown hypersensitivity to any of the components, and in herpes simplex, vaccinia, and varicella.
WARNINGS:
Prolonged treatment may result in overgrowth of nonsusceptible organisms and fungi. If the infection is not improved after one week, cultures and susceptibility tests should be repeated to verify the identity of the organism, and to determine whether therapy should be changed.

When using neomycin-containing products to control secondary infection in the chronic dermatoses, such as otitis externa, it should be borne in mind that the skin in these conditions is more liable than is normal skin to become sensitized to many substances, including neomycin. The manifestation of sensitization to neomycin is usually a low grade reddening with swelling, dry scaling, and itching; it may be manifest simply as a failure to heal. During long-term use of neomycin-containing products, periodic examination for such signs is advisable and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for that patient thereafter.
PRECAUTIONS:
If sensitization or irritation occurs, medication should be discontinued promptly. Patients who prefer to warm the medication before using should be cautioned against heating the solution above body temperature, in order to avoid loss of potency.

Treatment should not be continued for longer than ten days. Allergic cross-reactions may occur which could prevent the use of any or all of the following antibiotics for the treatment of future infections: kanamycin, paromomycin, streptomycin, and possibly gentamicin.
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SUPPLEMENT 52 – VOL. 87, SEPTEMBER-OCTOBER, 1978, NO. 5, PART 2

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FIBROUS HISTIOCYTOMA OF THE TRACHEA

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BENJAMIN H. LANDING, MD HART ISAACS, MD
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Intratracheal tumors are rare in children. A case is reported of a two-year-old female child with a fibrous histiocytoma of the trachea which caused severe respiratory obstruction and persistent right middle lobe pneumonia. Fibrous histiocytomas are basically benign tumors of histiocytes and have been mistaken for other tumors such as fibroma, sclerosing hemangioma, neurilemoma, fibromatosis, hemangiopericytoma, fibrosarcoma, and some primitive sarcomas. Fibrous histiocytomas have not been reported in the trachea or bronchi. The patient was treated with endoscopic removal of the tumor, and has remained free of disease to this date.

Intratracheal tumors are rare in children. MacLachlan[1] reported a case of tracheal fibroma in a child age 21 months, and he reviewed the literature in 1968. Gilbert et al,[2] analyzed 546 cases of primary intratracheal tumors in children and adults. Only 43 occurred in children; 40, nonmalignant; and 3 sarcomas (all in girls). The benign tumors included 23 papillomas, 9 fibromas, 6 angiomas, and 1 osteochondroma; no cases of xanthofibroma were included in this review.

Fibrous histiocytomas are rare tumors of histiocytes, not associated with generalized lipid metabolic defect, most often found in skin, tendons, joints, and soft tissues. A few cases have been reported in the lungs,[3] Rolander et al,[4] have reported a fibrous xanthoma of the larynx, and this report describes xanthofibroma of the trachea in a two-year-old girl.

Kaufman and Stout[5] believe that these are basically tumors of histiocytes, and have divided them into two groups, depending on their content of fibroelastic tissue. Those with more fibrous tissue are called fibrous xanthoma, and those with less, histiocytoma.

Fibrous histiocytomas are usually benign; removal of large amounts of normal tissue is not necessary.

Fibrous histiocytoma can be mistaken for a number of other tumors, including fibroma, sclerosing hemangioma, neurilemoma, fibromatosis, hemangiopericytoma, fibrosarcoma, and some primitive sarcomas. Of examples of fibrous histiocytomas in the literature, none occurred in the trachea or bronchi, and only one in the lung. Five of the malignant or questionably malignant fibrous xanthomas were on the trunk or extremities. One of these patients died, and the others had recurrences.

CASE REPORT

W.M., a female Caucasian, was born on October 10, 1966. The mother's pregnancy and child's birth history were completely normal. The infant apparently was perfectly normal until July, 1968, when she was admitted to another hospital with an upper respiratory infection, fever to 40 C, and seizures. X-ray of the chest was reported to have shown "bronchitis without pneumonia." She was treated with phenobarbital and Dilantin®, and from September to October, 1968, had intermittent tachypnea and fever, attributed to upper respiratory infection. On October 29, 1968, she was readmitted to the outside hospital with nonproductive cough and fever. Throat culture showed *Staphylococcus aureus* (coagulase-positive) and she was treated with antibiotics, Decadron®, and expectorants. She was evaluated for allergy, but all studies were negative. During September and October she was treated with gammaglobulin without change in her symptoms, and increasing

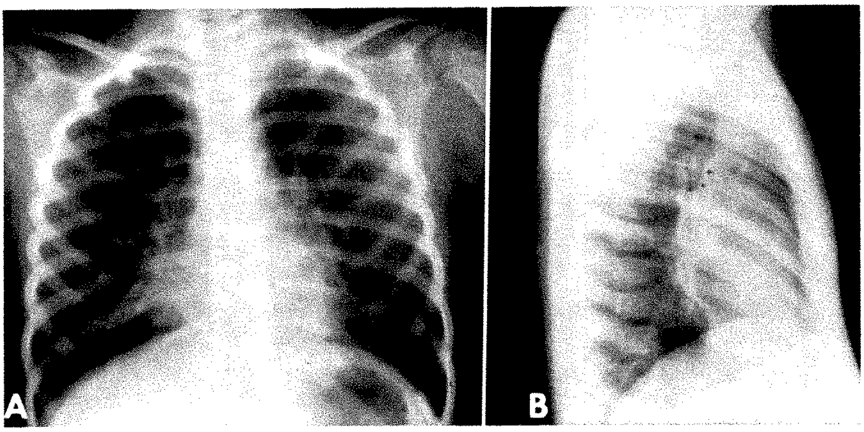

Fig. 1. A) Posteroanterior view of the chest shows the right middle lobe pneumonia with bilateral hyperaerated lungs. B) The lateral film shows the outlined mass obstructing the trachea at the level of the carina.

difficulty in breathing, plus coughing with low grade fever, refractory to antiasthmatic medication, resulted in her admission to Childrens Hospital of Los Angeles (CHLA) on November 29, 1968. She was a well-developed, well-nourished Caucasian female, with respirations of 60/min, pulse rate of 140/min, temperature 37.7 C, rhonchi in the right base, and some xiphoid retractions. Ear, nose, and throat were normal. Hemoglobin was 13.5 gm%, and WBC was 9,200/mm^3, with 62% segs; urinalysis and sweat tests were normal. A tine test and spinal puncture were normal. Roentgenogram of the chest revealed right middle lobe left lingular segmental pneumonitis (Fig. 1A). A barium esophagram was reported as normal. Her initial treatment was with intravenous penicillin and fluids, but methicillin was given because throat cultures showed a staphylococcus resistant to penicillin. On December 4, 1968, she developed meningismus, but again, a lumbar puncture showed normal spinal fluid. The diagnosis was changed to probable viral pneumonitis, and all antibiotics were discontinued. She seemed to improve, until December 12, 1968, when she suddenly developed severe tachypnea and respiratory distress. Fluoroscopy revealed what was interpreted as a foreign body at the carinal level, best seen with the patient in Trendelenberg's position at 60° (Fig. 1B). Direct laryngoscopy under general anesthesia revealed the larynx to be perfectly normal, and vocal cord mobility was normal. There was no evidence of infection or obstruction. Bronchoscopy showed the trachea to be normal, but at its lower end, there was a smooth yellowish tumor occluding the lower end trachea, with a 1 mm passage anteriorly The right mainstem bronchus was almost completely occluded. Ma-

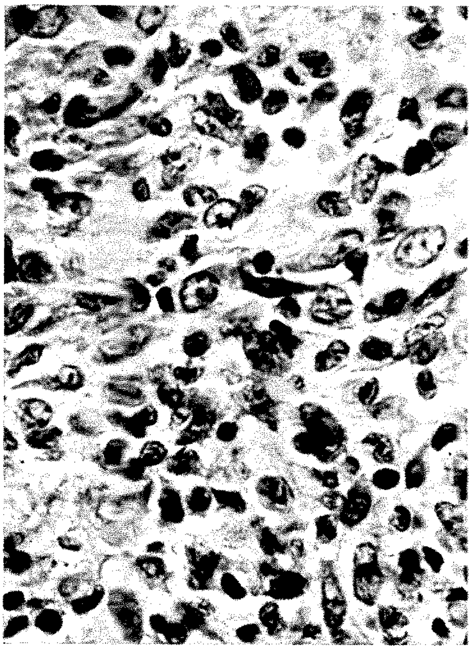

Fig. 2. Fibrous histiocytoma of trachea, showing admixture of vacuolate and spindle-shaped histiocytes. (H & E, X120)

nipulation of the pedunculated mass showed it to arise from the right side of the trachea, just above the carina. The mass was removed piecemeal, with forceps, with minimal bleeding, leaving the small pedicle of the tumor mass which arose from the lateral wall of the trachea. The patient's airway postoperatively was excellent, and her immediate course was uneventful.

On December 18, 1968, bronchoscopy was repeated, and remnants of the tumor were removed. She was discharged on December 20, 1968, and has been free of symptoms to this date.

Pathology. The specimen (Fig. 2) consisted of several yellow nodules, the largest fragment measuring 8 x 5 x 5 mm. Frozen sections were interpreted as consistent with xanthofibroma, and permanent sections revealed proliferating fibroblasts and foamy macrophages, partially covered by keratinized, stratified squamous epithelium. The lesion was moderately vascular, and was infiltrated by neutrophils. The fibroblasts possessed round or oval nuclei with prominent nucleoli, and spindle-shaped eosinophilic cytoplasm. The histiocytes had small round nuclei and pale, foamy cytoplasm. Mitoses were rare to absent. The lesion was diagnosed as benign xanthofibroma of the trachea, a term now considered to be a synonym of fibrous histiocytoma.

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LYMPHOMATOID GRANULOMATOSIS IN A CHILD WITH ACUTE LYMPHATIC LEUKEMIA IN REMISSION

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Lymphomatoid granulomatosis, a tumor-like process of unknown etiology, produced progressively destructive disease of the larynx, trachea and bronchi in an eight-year-old girl with acute lymphoblastic leukemia of five years duration. The leukemia had been in remission for 4½ years at the clinical onset of the lymphomatoid granulomatosis. Whether this occurrence suggests that lymphomatoid granulomatosis is a type of neoplasm, or is associated with immunologic depression, cannot be stated. Fortunately rare, and of poor prognosis, the disorder may become more frequent with improved survival rate of patients with leukemia and other neoplasms.

Lymphomatoid granulomatosis[1] is defined as an angiocentric, angiodestructive, lymphoreticular granulomatous disease, involving predominately the lungs but often affecting skin, kidney, nervous system, liver, and heart, and tending to spare lymph nodes, spleen and bone marrow. The infiltrate is polymorphous, with varying numbers of cells in mitosis, and may contain atypical, especially plasmacytoid, cells of reticuloendothelial origin.

Rarely generalized atypical lymphoid hyperplasia may precede the onset of pulmonary lesions, sometimes by many years.

Some patients respond well to treatment, but 26 of the original 40 reported by Liebow et al[1] died, 14 as a consequence of involvement of the lungs. Massive hemorrhage from cavitary lesions caused death in three. In six, pulmonary lesions healed and death occurred from CNS disease or other involvement. Six of 14 survivors lived more than four years after diagnosis of the disease, and 4 are apparently free of disease, with survival credited to steroid therapy in 3. One patient survived eight years with no treatment.

Fienberg[2] first introduced the concept of Wegener's granulomatosis limited to the lungs, which he called "Limited Pathergic Granulomatosis." Wegener himself is said to doubt the concept of a limited form of the disease, and Liebow et al feel that lymphoid granulomatosis is akin to, but separate, from limited Wegener's granulomatosis, the absence of glomerulitis and the presence of atypical lymphoid cells in lymphomatoid granulomatosis setting it apart from Wegener's granulomatosis.[1,3]

While Liebow considers the cellular infiltration of blood vessel walls in lymphoid granulomatosis as angiitis, it may possibly represent neoplastic infiltrate.

In lymphomatoid granulomatosis lesions typically involve the peripheral lungs, chiefly in the lower lobes with sparing of the apices. Extrapulmonary sites include skin and subcutaneous tissue, kidneys and, less commonly, liver, adrenal, and CNS. In no instance has the renal lesion been a focal glomerulitis, as in classic Wegener's granulomatosis.

Reported ages range from 8½ years to 70 years, with two thirds of the patients males between the ages of 15 and 40 years.[4]

CASE REPORT

D.C. was a 3½-year-old Caucasian female who was first seen in July, 1972, with a history of progressive pallor and lethargy over a period of two months with a one week history of spiking fevers and recurrent epistaxis with bruising tendencies. Her initial peripheral blood counts showed the hemoglobin to be 4.2 gm%, the white blood count to be 2,800/cu mm with 98% lymphocytes and 2% monocytes. A platelet count was less than 5,000/cu mm. A diagnosis of acute lymphoblastic leukemia was confirmed by bone marrow aspiration, and she was placed on initial chemotherapy induction with vincristine 1.5 mg/M^2/wk IV, prednisone 40 mg/M^2/day po, and L-asparaginase 6,000 units/M^2 IM three times a week for a total of nine doses. She was continued on this therapy for a period of four weeks at which time a bone marrow aspirate revealed a complete remission.

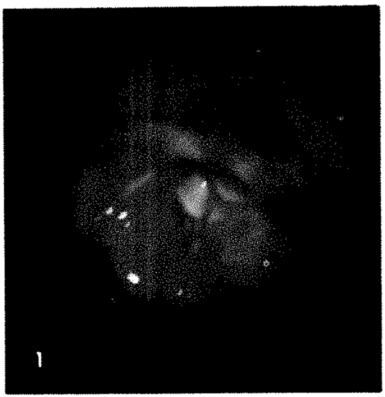
The patient was then treated with irradiation to the brain and spinal axis (2400R) as well as liver, spleen, and gonadal areas (1200R) as a part of a prophylactic program to prevent the recurrence of leukemic disease in these known sanctuaries. She tolerated this therapy well and on October 27, 1972, maintenance chemotherapy was ordered which consisted of vincristine 1.5 mg/M^2 IV once monthly, prednisone 40 mg/M^2/day po for five days, given once monthly, 6-mercaptopurine 75 mg/M^2/day po and methotrexate 25 mg/M^2/wk po. Bone marrow aspiration showed continued remission status. Because of recurrent leukopenia on this maintenance program, her methotrexate dose was reduced to 10 mg/M^2/wk and her 6-mercaptopurine was reduced to 50 mg/M^2/day.

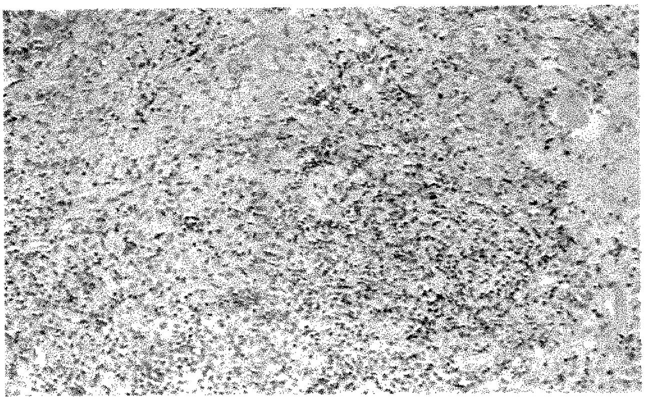
She continued on this maintenance program without evidence of recurrence for the next 4½ years. The patient continued to have during this period of maintenance chemotherapy, intermittent chronic cough without evidence of pulmonary changes by x-ray. One episode of documented pneumonia in November, 1974, required oral antibiotics. In December, 1975, she was treated with oral antibiotics for a staphylococcal infection of the right thumb.

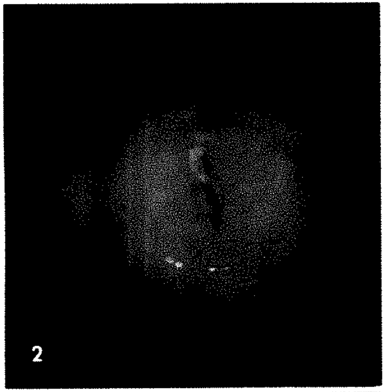
In February, 1977, she received penicillin therapy for a right acute otitis media with resolution of the infection. Recurrence of middle ear infection in April, 1977, and again in May, 1977, required antibiotic therapy.

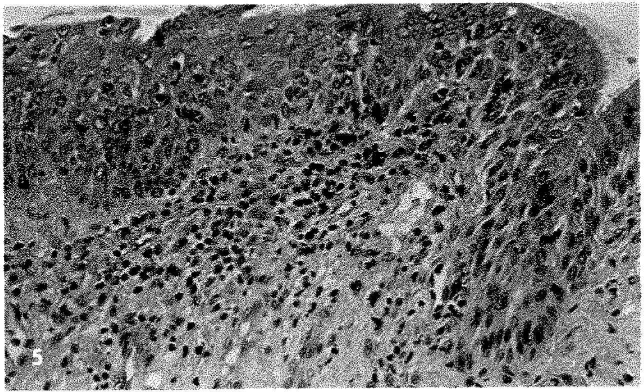
In June, 1977, associated with a left otitis media, there was a minimal infiltrate in the left lingula. On August 15, 1977, because of otitis media with perforation due to staphylococcal and hemophilus infections, she was admitted to CHLA for therapy. This admission was associated with spiking fever and chills with a productive cough. There was no tachypnea, chest pain, cyanosis or skin rash. Physical examination revealed an alert, comfortable, young child in no acute distress. Her temperature was 39.9 C orally, the pulse was 128/min and the respiratory rate was 36/min. Bilateral expiratory wheezing was heard at both lung bases and moist rales at the right base. Bilateral persistent otitis media was noted which had apparently not responded to oral antibiotic measures. Laboratory data showed the hemoglobin to be 12.3 gm %, white blood count of 4,900/cu mm with 78% segs, 2% bands, 14% lymphocytes, 3% monocytes, 1% eosinophils and 2% basophils with a normal platelet estimate. An x-ray of the chest revealed a right middle lobe and left lower lobe patchy infiltrate with a left small pleural effusion. Blood cultures and throat cultures showed no significant pathogens and she was given intravenous penicillin therapy. Bilateral myringotomies were performed and a culture revealed a *Staphylococcus aureus* (coagulase positive, resistant to penicillin), and the patient was given intravenous methicillin therapy. Within 48 hours she became afebrile and she was discharged on oral dicloxacillin to be followed as an outpatient. Anti-leukemic therapy was discontinued.

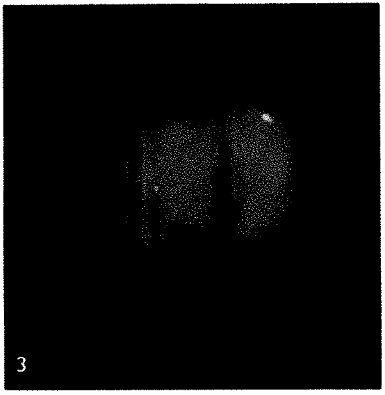
The patient remained afebrile, but the cough and otitis media persisted until she was readmitted on August 30, 1977, with the x-ray findings of progression of the left lower and right middle lobe infiltrates. Her peripheral blood count was within normal limits and the platelet count was 435,000/cu mm. Cold agglutinin titer was negative. She was











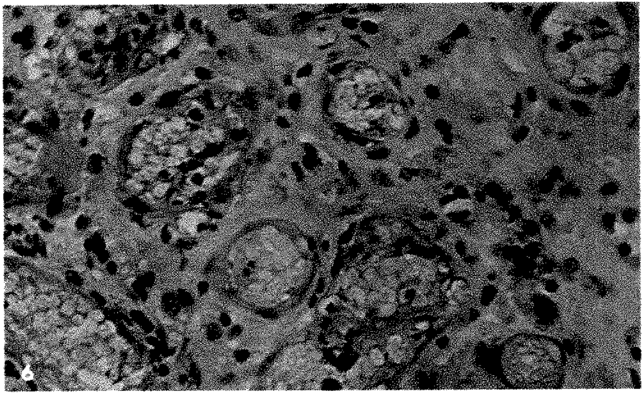


Fig. 1. Laryngoscopic view showing the necrotic polypoid mass anteriorly and severe infiltrating lesion of the larynx narrowing the airway. The granulomatous necrotic process extended throughout the trachea and left bronchial tree.

Fig. 2. Laryngoscopic view showing recurrence of necrotic mass anteriorly after removal, but less inflammation and infiltration.

Fig. 3. Photograph of larynx following multiple doses of steroids (Decadron®).

Fig. 4. Lymphomatoid granulomatosis, showing infiltration by lymphoid cells and extensive necrosis. (H & E X75)

Fig. 5. Bronchial biopsy showing atypical cellular infiltrate beneath metaplastic epithelium. (H & E X75)

Fig. 6. Lymphomatoid granulomatosis, showing capillary proliferation, cellular infiltrate and fibrous reaction in deeper tissue. (H & E X190)

given intravenous Keflin® and gentamicin therapy and vigorous pulmonary toilet, but because of persistent spiking temperatures, bronchoscopy was recommended on September 16, 1977. A PPD, coccidioidomycosis skin test, microplasma titer, urine for cytomegalovirus were all reported as negative.

On September 26, 1977, with persistent pulmonary findings and fever, and increasing respiratory obstruction with to and fro stridor, direct laryngoscopy and bronchoscopy were performed. An infiltrating granulomatous lesion of the larynx, immediate subglottic area and tracheobronchial tree with almost complete occlusion of the left mainstem bronchus just below the upper lobe bronchial take-off, was noted (Fig. 1). A biopsy of the granuloma tissue from the larynx and tracheobronchial tree revealed necrotic tissue containing inflammatory cells, but with no evidence of specific organisms (Fig. 4). Acid-fast bacteria and *Pneumocystis carinii* pneumonia were not identified in the sections of the granuloma tissue. Immediately postoperatively she was given a large dose of intravenous Decadron® to reduce possible increased swelling in the larynx, and some improvement in the obstruction was noted for only a short period of time. Following the biopsy and lavage of the bronchial tree, the patient continued to be afebrile with improvement in the radiographic findings and clinical symptomatology.

Intravenous ampicillin was discontinued on October 6, 1977, at which time a persistent left lower lobe infiltrate was noted at the left base with lower lobe atelectasis. The patient developed increasing cough with bilateral expiratory wheezes with inspiratory and expiratory stridor, and direct laryngoscopy and bronchoscopy were repeated on October 10, 1977. Findings in the larynx and tracheobronchial tree were similar to those found at the previous endoscopic procedure (Fig. 2). Biopsy of the larynx revealed a necrotizing laryngitis and infiltration of the larynx by atypical lymphocytes and inflammatory cells which were interpreted as possible leukemic infiltration of the larynx. The trachea and left lower lobe bronchial biopsy showed chronic inflammation and squamous metaplasia with intermixed granulation tissue (Fig. 5). No specific causitive organism was identified on these biopsies. Prior to endoscopy, x-rays of the paranasal sinuses showed bilateral maxillary sinusitis, but no specific treatment was given for this finding. Oral penicillin was advised and then, because of an exacerbation of respiratory obstruction and to attempt to obtain more tissue for specific diagnosis, endoscopy was repeated on October 12, 1977. Laryngeal biopsy at this time revealed a necrotizing process with infiltration of the larynx by inflammatory cells, large reactive histiocytes and a number of atypical cells with large nuclei and prominent nucleoli which were felt to be consistent with lymphoblasts. The biopsy of the left lower lobe bronchus showed chronic inflammation and squamous metaplasia similar to that found on previous endoscopic biopsies (Fig. 6). Again, as following each endoscopic procedure a large dose of intravenous Decadron® was given to prevent increased obstruction to the airway and the procedures were tolerated very well with improvement in the airway obstruction (Fig. 3). However, x-rays revealed a persistence of the left lower lobe pneumonia with infiltrate in the right lower lobe and cyst-like changes at the left base (Figs. 7 and 8). She was continued on oral pencillin until cultures revealed a *Hemophilus influ-*

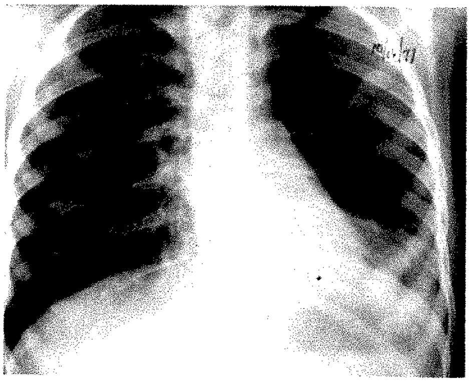


Fig. 7. Roentgenogram of chest showing the consolidation of the left lower lobe with pneumatocele formation.

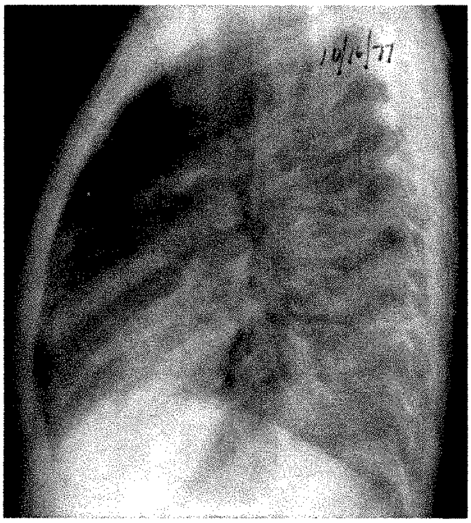


Fig. 8. Lateral roentgenogram of chest showing the infiltrate in lower lobe and cystic changes.

enza not A or B, after which intravenous ampicillin was started.

Because of the persistence in pulmonary findings, skin tests for coccidioidomycosis, mumps, tuberculosis and candida were all performed and found negative. Blood cultures were performed because of spiking temperatures to 39 C and were found positive for *H. influenza* not A or B sensitive to ampicillin.

Because of persistent spiking fevers, further blood cultures showed bacteroides species. Serum immunoglobulins showed a decreased IgA and IgG with normal levels of IgM.

On October 24, 1977, hemoptysis with a loss of approximately 300 cc of blood occurred with precipitous drop in blood pressure, but stabilization was possible with Albumisol® and whole blood transfusion. Chloramphenicol and ampicillin were given intravenously and further tests at this time showed C3 complement level of 104 (normal = 53-125), C4 28 (normal = 20-50), IgM 438 mg%, (normal=77-288 mg%), IgA 24 mg%, (normal = 61-336), and IgG 435 (normal = 725-1988). Repeat blood cultures showed persistence of *Bacteroides fragilis* in the anaerobic bottle.

On October 27, 1977, the patient had an episode of severe hemoptysis of over 500 cc; cardiorespiratory arrest resulted and she could not be resuscitated. Blood cultures obtained on the day before her death showed no evidence of bacterial growth. A bone marrow aspirate was obtained on October 4, 1977, revealing a hypercellular marrow with a marked increase in late myeloid precursors and no evidence of leukemic infiltrate.

Pathology. Gross autopsy showed multiple ulcerative and destructive lesions of the larynx, right laryngeal ventricle, upper and lower trachea, left and right main stem bronchi. The left lower lobe bronchus was dilated to a 6 x 4 x 4 cm cavity filled with dark brown necrotic material and fresh blood clot. A small artery was pointing into the lumen. The left lung contained numerous 1-2 cm, pink-tan, firm nodules, some with a small central opening of a vessel or bronchiole. A lesion in the lingular lobe was cavitated. The right lung showed massive aspiration of blood.

Microscopically, the destructive airway and pulmonary lesions consisted of a pleomorphic mononuclear infiltrate with coagulative necrosis, fibroblastic and endothelial proliferation. The cells were atypical lymphocytes, plasmacytoid cells, atypical histiocytes, foamy histiocytes and some plasma cells. Reed-Sternberg cells, Langerhans' giant cells and eosinophils were not found. Mitotic figures were rarely seen. The pulmonary nodules were all centered around bronchii and bronchioles. The arteries and veins were involved frequently. Bacteria and fungi were seen in the necrotic tissue in the trachea and bronchi. No organisms were found in the lung nodules. Postmortem lung and tracheal cultures grew *H. influenza,* and streptococcus, *Candida albicans, B. fragilis* and other anaerobic organisms. Blood culture grew *B. fragilis* and peptostreptococcus.

No similar lesions were seen in the kidneys, brain and other organs. No evidence of leukemia or lymphoma was found in bone marrow, lymph nodes and spleen. Other significant findings were hepatic periportal fibrosis and fatty change (postchemotherapy), adrenal atrophy and thymic involution.

The lesions observed were a form of pulmonary angiitis and granulomatosis with moderately atypical lymphohistiocytic proliferation and appeared to be both bronchocentric and angiocentric. The histology, sites of involvement and clinical features do not precisely match with any of the five types of pulmonary angiitis and granulomatosis classified by Liebow in 1973. The aggressive behavior of the cellular infiltrate suggests that it is closely related to lymphomatoid granulomatosis. The pathologic diagnosis is pulmonary angiitis and granulomatosis, probably lymphomatoid granulomatosis, multiple, larynx, trachea, bronchi and left lung.

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SOLITARY PLASMACYTOMA OF THE LARYNX AND UPPER TRACHEA ASSOCIATED WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Solitary plasmacytoma rarely involves the larynx and trachea. This tumor caused severe laryngeal and tracheal obstruction in an adolescent female with systemic lupus erythematosus of nine years' duration. Her systemic disease had been in remission at the time she developed symptoms of laryngeal and tracheal obstruction by plasmacytoma invasion. A complete survey failed to reveal any other focus of tumor. Because steroid therapy failed to clear the plamsa cell infiltrate, she was treated with irradiation after the tumor was surgically debulked endoscopically. Postirradiation biopsy showed no evidence of tumor, but the patient continued to experience moderate airway obstruction from fibrosis in the irradiated trachea. The patient has been followed, and is free of disease nine years after establishing the diagnosis.

Clinically, laryngeal involvement in systemic lupus erythematosus (SLE) has been considered unusual. Dubois[1] in studying or reviewing 520 patients, could find only 2 with laryngeal symptoms attributable to the underlying disease, and Toomey[2] could find only 13 recorded cases of acute laryngitis due to SLE.

Seventy-five percent of soft tissue plasmacytomas arise in the upper respiratory tract and oropharynx. Gorenstein, et al[3] reported that since Schriddele reported the first case of extramedullary plasmacytoma in 1905, 250 cases have been reported in the English literature. These tumors occur in the airway, gastrointestinal tract and soft tissues, and are indistinguishable histologically from those occurring in bone marrow. The tumor occurs in men three times more often than in women and is seen in the age group 50-70 years. They report 6 patients with extramedullary plasmacytoma of the larynx as a solitary tumor (1949-1974), from a period when 3,100 patients with malignant laryngeal neoplasms were examined. Excision, electrocoagulation, irradiation, or some combination of these, constituted effective therapy and extensive surgery was rarely necessary. The youngest patient reported was 32 years old, and the oldest 63 years of age.

Of 161 cases of extramedullary plasmacytoma reviewed by Dolin and Dewar[4] 78% were in the head and neck area. These authors point out that the primary lesion will often be seen first by the otolaryngologist. In the larynx the lesion is most likely to be pedunculated and to be more common in females.

Petrovich, et al,[5] in a review of extramedullary plasmacytosis of the upper respiratory tract over the period 1947-1976, found only seven cases, of which one occurred in the epiglottis. They felt that radiation gave the best functional, cosmetic, and tumor control.

CASE REPORT

J.C., a Caucasian female, born September 15, 1954, first presented at CH LA on May 22, 1961. In November of 1960, she developed vesicular lesions around the knees and along the medial surface of the legs, with joint swelling of the right knee. For three months, she had had red elevated lesions which then became vesicular on the knees, fingers, buttocks and ears. For the past seven months she had complained of painful shoulders, elbows, fingers and knees which felt swollen at times. Physical examination revealed fading papules on the arms, buttocks and legs and hard raised hemorrhagic crusted lesions on the ear lobes. Large left axillary and inguinal lymph nodes were palpable. Ulcerated lesions were seen in the mouth. The liver was palpable 1 cm below the right costal margin. The right knee was tender, swollen, warm and had limitation of motion. Her vital signs were normal, the LE preparation was positive, a sedimentation rate of 70 mm (Westergren), BUN was 24, and the blood count showed an anemia of 9.4 gm% with a WBC of 8,000. The urine examination showed 4 plus albuminuria with 9-12 WBCs and many RBCs and fine and course casts.

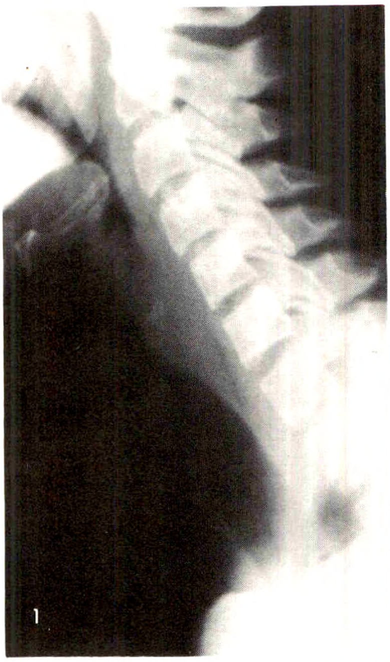
A renal biopsy showed focal glomerulonephritis and the patient was started on prednisone 75 mg/M^2 (54 mg/day) in four divided doses. She was continued on this dose for three weeks and then the steroid was tapered. Chloroquine was then added at doses of 125 mg/day. The rash and arthritis disappeared. Prednisone was discontinued in September, 1961, and the chloroquine was stopped in December, 1963. Gradual reduction of urinary findings occurred, and by May of 1962, there were no red cells, although the patient continued to have one and two plus proteinuria. ANA was negative in August, 1964. (This was the first time this test was done at CHLA.)

In November, 1964, the ANA became positive and has remained so. In December, 1964, because of intermittent rashes, she was started on Plaquenil® in doses of 200 mg/day. This drug was discontinued in September, 1966.

The patient remained well until June 30, 1969, when she was admitted to CHLA because of progressive respiratory difficulty over a period of approximately two months. A previous indirect laryngoscopy had revealed a laryngeal obstructive tumor mass in the immediate subglottic and upper trachea. Laboratory findings on this admission, including an x-ray of the chest, were all within normal limits. A lateral x-ray of the neck showed narrowing of the subglottic lumen (Fig. 1). A direct laryngoscopy under general anesthesia revealed a large, sessile, smooth, subglottic tumor mass invading the entire left half of the subglottic larynx. The lesion was noted to extend to the posterior commissure, narrowing the airway to less than one half of its normal size (Fig. 3). The vocal cords and supraglottic laryngeal areas were perfectly normal. Mobility of the vocal cords was also found to be normal. Biopsies were taken of this very hard tumor infiltrating lesion. Very little bleeding occurred, and the patient tolerated the procedure well. She was discharged awaiting biopsy report.

The biopsy was reported as a benign plasmacytoma (Fig. 4), and she was readmitted on July 16, 1969, for attempts at removal of the tumor to improve her airway. Following removal by direct laryngoscopy of the infiltrating tumor mass, her airway improved and she was discharged on the following day. Prednisone, 90 mg/day po was given to attempt to reduce the plasma cell infiltrate, believing this was possibly related to her disseminated lupus erythematosus. She improved somewhat until October 14, when she was again seen with the complaint of difficult breathing with any physical activity. The obstruction to the airway increased and direct laryngoscopy was again carried out on October 20, 1969. The biopsy at this time showed fewer plasma cells, with increased histiocytes and increased fibrosis, apparently a result of steroid therapy.

Because of increasing respiratory obstruction, irradiation therapy was advised. A tumor dose to the area of the plasmacytoma at the anterior margin of the cervical spine of 4000 rads was delivered within a 30 day period. The radiation was delivered, using cobalt 60 with a single anterior port of 2900 rads and then an additional 1100 rads added through lateral laryngeal ports. Therapy was completed on January 8, 1970. The treatment port extended from the top of the thyroid cartilage to the sixth tracheal ring.



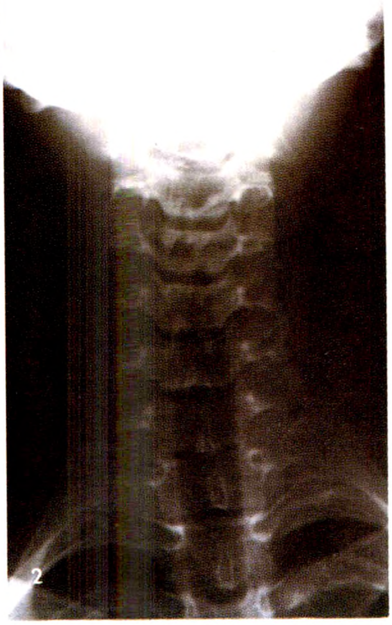
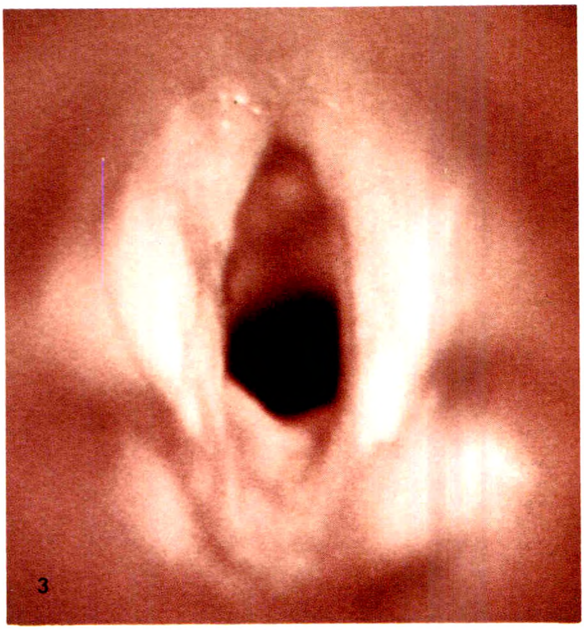


Fig. 1. Lateral roentgenogram of the neck showing mass in the subglottic and upper tracheal area narrowing the airway.

Fig. 2. A-P view of the neck showing the narrowed trachea and subglottic area. The cervical spine is normal.



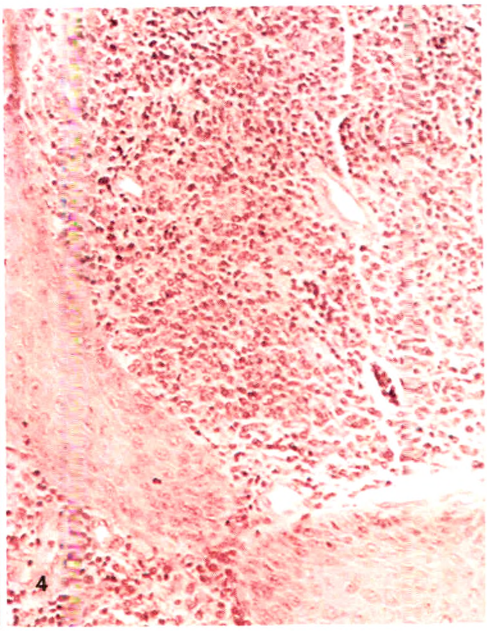


Fig. 3. View of the larynx showing the subglottic tumor encircling the larynx and upper trachea. The supraglottic larynx is normal.

Fig. 4. Plasmacytoma of larynx, showing massive infiltration of subepithelial tissue by plasma cells and occasional lymphocytes, with no significant fibrosis. (H & E, X75)

Improvement was noted in her airway, but the subglottic narrowing persisted. At no time were any neck masses palpable, and a bone survey was found to be negative for disease.

In November, 1970, because of increasing airway obstruction with irregular narrowing of the upper trachea, prednisone in doses of 80 mg orally was given every other day. Obstruction persisted and on November 18, 1970, laryngoscopy, bronchoscopy and biopsy and a tracheotomy were performed. The biopsy showed no evidence of tumor. During this admission, her complete blood count was normal, bone marrow examination showed no abnormal cells, and a sedimentation rate of 53 mm. Alkaline phosphatase was found to be 1.5 units with beta 1 C globulins 135 mg% with slightly decreased IgG and IgA levels.

A biopsy of the larynx and trachea in March, 1971, again showed no evidence of plasmacytic infiltrates, and the pathology diagnosis was one of chronic laryngitis with fibrosis. By April, 1971, the tracheotomy tube was removed and she continued to have respiratory obstruction with stress of exercise. Repeated examinations showed the larynx to be normal without evidence of tumor, but the trachea was narrowed presumably due to irradiation fibrosis (Fig. 2). Since then, the patient has had periods of moderately severe respiratory obstruction occurring in conjunction with respiratory infections. Crusting in the irradiated areas occurred with each infection, requiring humidification and treatment with antibiotics. She has been followed in the Rheumatology Clinic and is known to be free of tumor, but with persistent tracheal stenosis.

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WEGENER'S GRANULOMATOSIS CAUSING LARYNGEAL AND TRACHEOBRONCHIAL OBSTRUCTION IN AN ADOLESCENT GIRL

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A 12-year-old girl presenting with a painful neck mass and ulcerated gingival lesions was found to have Wegener's granulomatosis involving the gingivae, paranasal sinuses, ears, mastoids, larynx, trachea, bronchial tree, lungs, kidneys and joints. The initial illness and two subsequent exacerbations were treated with intravenous and oral cyclophosphamide and prednisone. Secondary infections have been managed with establishment of good drainage and use of appropriate antibiotics. The patient is well with a normal sedimentation rate 4½ years after the onset of her disease.

Since its description by Wegener in 1936,[1] hundreds of cases of Wegener's granulomatosis have been reported, approximately a dozen in children. At one time invariably fatal within months, the disease may, with immunosuppressive drugs be thrown into remission or even, at times, appear curable. Taberman[2] reported a 39-year-old female who developed laryngeal obstruction in spite of prednisone therapy, and who required a tracheotomy. Irradiation produced a good response in the larynx, but the patient died of renal failure. For the disease to produce severe laryngeal and tracheobronchial obstruction in a child has not hitherto been reported.

The case herein reported is that of a 12-year-old girl with the generalized form of the disease, in whom severe obstruction of the airway required endoscopic removal of obstructive granulomata.

Wegener's granulomatosis is a diffuse systemic disease of unknown etiology.[1,3] Classically, it includes a triad of necrotizing granulomatous lesions in the upper or lower respiratory tract or both, generalized vasculitis involving arteries and veins, and focal necrotizing glomerulitis.[4] Limited forms of the disease have been described,[5,6] with the term applying to patients with lungs primarily affected, and without evidence of renal involvement. This form appears to respond to steroid therapy, and survival may be prolonged. Of four such patients reported by Cassan,[6] one was an 11-year-old boy. The pathogenesis has been proposed to be an immunological disorder occurring as a result of a granulomatous reaction to an external, possibly microbial agent which breaks down pulmonary tissue and creates a systemic autoimmune reaction.[5] The entity known as lethal midline granuloma has been regarded by some as one end of the continuum of the disease,[7,8] but because of differences in histologic findings and in response to therapy, others [9,10] regard midline granuloma as a separate entity. The term has probably been used in the past to include the patients who had Wegener's granulomatosis,[7] and confusion still exists concerning the interrelationship of the two entities.

Wegener's granulomatosis most commonly affects persons of either sex in the fourth and fifth decades. Two recent reports[11,12] listed cases reported in children 16 years of age or less, and add three new cases to the pediatric literature. One child was three months old at the onset of disease, but most were over ten years old. The earliest symptoms are usually referable to the respiratory tract, with rhinorrhea and sinus pain as the most common presenting symptoms, but fever and anorexia, weight loss, cough, chest pain and arthralgia are also frequent.[13] Pulmonary lesions may be detected at the time of presentation by chest x-ray, or may appear later. There may be solitary or multiple nodular densities or infiltrates, with or without cavitation. Pulmonary abnormalities may be fleeting or transient, whereas renal disease, once established, tends to progress relentlessly from proteinuria, hematuria and red cell casts, to renal insufficiency.[13] Other loci involved by granulomatous disease and vasculitis include eyes, ears, skin, muscles, heart, and nervous system. Anemia, which may be profound (7-8 gm) during active disease, leukocytosis, elevated sedimentation rate, elevation of alpha 2 globulin and immunoglobulins and microangiopathic hemolytic anemia are described in many reports.

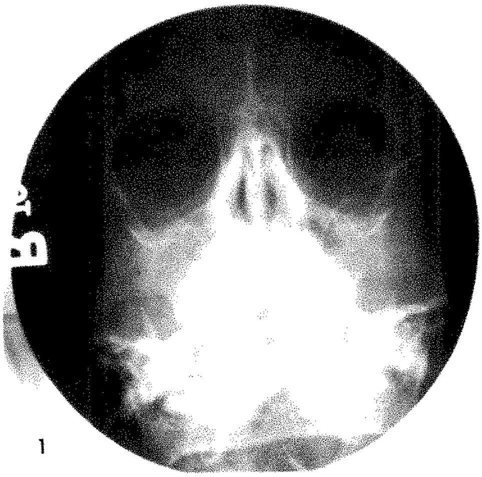
Secondary infection, particularly of the paranasal sinuses, may complicate the course of Wegener's granulomatosis, and it may be difficult to determine whether fever, elevated sedimentation rate and general malaise are due to infection or to active Wegener's granulomatosis.

The average survival time of untreated patients with Wegener's granulomatosis is reported as five months, with 93% dying within two years.[14] Upper respiratory lesions seem to respond to corticosteroid treatment early in the disease, but steroids alone are inadequate to control generalized disease. Several authors have reported noticeable improvement with the use of cytotoxic drugs in adults. Cyclophosphamide has been the most widely used immunosuppressive agent,[15,16] with uniformly good results, and with reported remissions lasting up to seven years. The drug has been used with and without concomitant corticosteroids. Because of its potent immunosuppressive properties, the problems inherent in using cyclophosphamide are significant. The possibilities of leukopenia and overwhelming secondary infection, alopecia, hemorrhagic cystitis, azoospermia and ovarian fibrosis, the as yet unknown potential for development of malignancies and for genetic damages, all prompt one to limit the use of the drug to control of active disease, and not to employ it for continued long-term maintenance therapy. Fauci et al[9] have suggested that treatment be individualized and that therapy be tapered and stopped one year after all traces of disease activity disappear in patients who experience prompt remission after treatment with the drug.

Three recently reported children have survived from 2½ to five years after treatment with cyclophosphamide. Our patient has survived 4½ years since the onset of disease, after treatment with cyclophosphamide.

CASE REPORT

R.W., a 12-year-old female, developed ulcerated lesions of the floor of the mouth in July, 1973. A biopsy in October, 1973, showed chronic sialadenitis. Following the appearance of a painful, submandibular mass and inflammation of the gingivae, she was admitted to CHLA on December 11, 1973. Physical examination revealed a moderately ill, adolescent girl weighing 42.5 kg, who had hypogeusia, hearing loss, and purulent drainage from the right ear and left nostril. There was an ulceration of the concha of the right ear. The parotid glands and neck were swollen, and a painful 7 x 7 cm right submandibular mass was palpable. The gingivae were severely inflamed with friable ulcerating masses. Respiratory wheezes and rhonchi were heard in the lungs. The hemoglobin was 10.6 gm%. WBC, urinalysis, and serum creatinine were normal. Rheumatoid factor was positive at 1:20 dilution and alpha 2 globulin was slightly increased. ANA, LE preparation, PPD, VDRL, and complement fixation tests for coccidioidomycosis and histoplasmosis were negative. Roentgenograms showed cloudiness of the right mastoid and mucosal thickening of the paranasal sinuses (Fig. 1). Cultures of purulent material from the right ear grew *Pseudomonas aeruginosa*. Biopsies of the neck mass, conchal lesion, right tympanic membrane, nasal septum, aural polyp, and the gingivae showed a suppurative granulomatous process with



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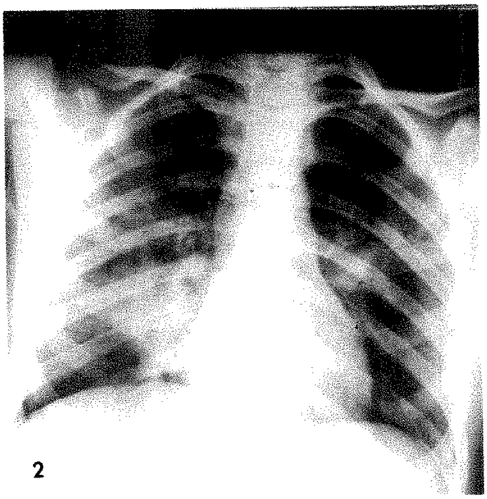

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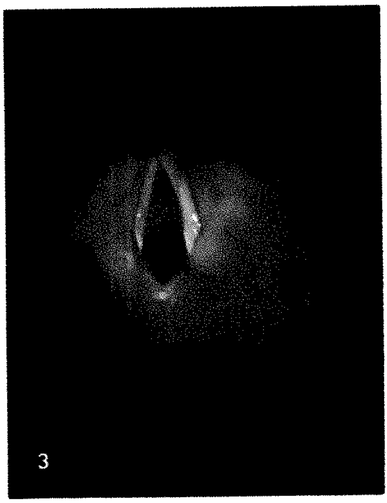
Fig. 1. X-ray of the paranasal sinuses showing marked opacification of the right maxillary sinus and mucosal hyperplasia in the left antrum.

Fig. 2. Roentgenogram of chest showing perihilar infiltrates with involvement of the right middle and lower lobe by infiltrates and pneumatoceles.



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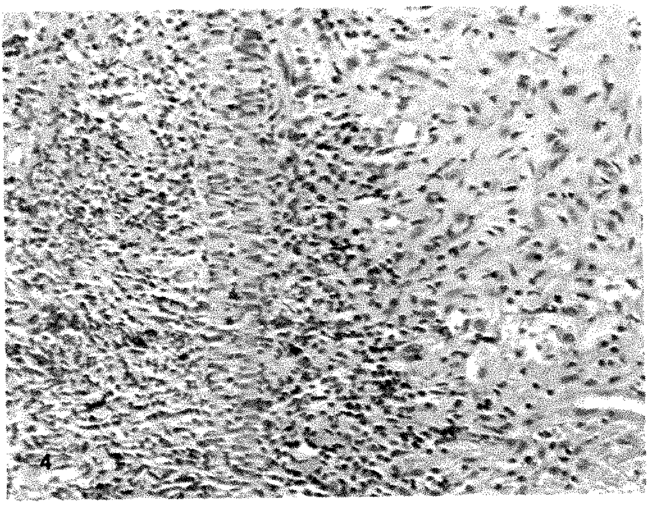

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Fig. 3. Endoscopic appearance of the larynx and upper trachea showing large granulomatous masses which extend throughout the trachea and both bronchi.

Fig. 4. Wegener's granulomatosis showing mixed inflammatory and fibrous process. (H & E X75)

many foreign body giant cells (Fig. 4). Special stains were negative for bacterial, fungal and acid-fast organisms.

The child developed stridor shortly after admission, and because of imminent airway obstruction, was treated with prednisone 60 mg/M^2/day. Gentamicin and intravenous cyclophosphamide 2 mg/kg/day for three days were given concurrently. The patient's condition improved dramatically, but within a few days microhematuria, proteinuria and granular and hyaline casts appeared. Renal biopsy showed extracapillary proliferative and necrotizing glomerulonephritis. Several days later the child complained of pleuritic chest pain and cough, and perihilar infiltrates were seen on chest x-ray. They progressed to involve the entire right lung, with formation of pneumatoceles in the lower lobe (Fig. 2). Necrotizing dermal granulomas appeared on the legs and elbows. Biopsies taken during laryngoscopy and bronchoscopy showed chronic suppurative bronchitis with foreign body giant cells. Ventilating tubes were inserted in both ears to facilitate drainage and to improve her hearing. After two more courses of intravenous cyclophosphamide at 3 mg/kg/day, oral cyclophosphamide, 125 mg/day was started and the prednisone dose was gradually tapered. The oral lesions healed, the neck mass disappeared, and the chest x-ray cleared within a few weeks. Hematuria gradually resolved during the following nine months.

In February, 1974, the patient complained of fever, arthralgia, abdominal and pleuritic pain, hoarseness and dyspnea. Dermal granulomata appeared on the face, elbows and legs, and a nasal septal perforation was noted. Pulmonary infiltrates were seen again on chest x-ray. Because of airway obstruction, laryngoscopy and bronchoscopy were performed. These showed the obstruction to be due to diffuse infiltrating granulomatous disease of the larynx, (Fig. 3) trachea, and bronchi. The lesions were cored out with the bronchoscope, with improvement in the airway. After three courses of intravenous cyclophosphamide at 5-7 mg/kg/day for three days each, all symptoms and signs of disease resolved. Oral cyclophosphamide, 200 mg/day, was continued along with prednisone 45 mg/day.

In July stridor was found to be due to subglottic, upper tracheal, and bilateral bronchial stenosis, with severe suppuration. For many months frequent laryngoscopies and bronchoscopies were necessary for dilation of stenotic areas to maintain airway patency. *Staphylococcus aureus* (coagulase-positive) was usually cultured from bronchial washings. There was no evidence of graulomata or giant cells on repeat biopsies, and cultures were negative for fungi and acid-fast bacilli. Severe left mainstem bronchostenosis led to persistent atelectasis of the left upper lobe and there were frequent episodes of pneumonitis, sinusitis, mastoiditis, and chronic otitis media, resulting in bilateral conductive hearing loss. In spite of this, the patient's condition improved steadily and cyclophosphamide and prednisone were discontinued in December, 1974.

In November, 1976, the child noted hypogeusia, hemoptysis, and gingival lesions similar to those present initially. Microscopic hematuria reappeared and the sedimentation rate was 108 mm/hr (Westergren). Multiple pulmonary infiltrates and cavities were seen on chest x-ray. A left mastoidectomy was performed because of persistent suppuration, and granulomatous disease of the mastoid was found. Laryngoscopy and bronchoscopy showed an anterior subglottic granulomatous lesion extending into the trachea, although only acute and chronic inflammation were present in histologic specimens. Two courses of intravenous cyclophosphamide were given, and oral cyclophosphamide was reinstituted in a dose varying from 50 to 150 mg/day, depending on the degree of leukopenia induced. Intermittent pulmonary infections and sinusitis were controlled with antibiotics, and the sedimentation rate dropped steadily to 16 mm/hr by April, 1977. By May, 1977, there was no hematuria, although proteinuria persisted throughout the course of the disease. The patient complained of bilateral lower abdominal pain, and the right ovary was found to be tender on pelvic examination. Biopsy showed ovarian fibrosis presumed to be secondary to cyclophosphamide therapy. Cyclophosphamide was discontinued in November, 1977, when the sedimentation rate was 19 mm/hr and the patient has been well since then.

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PRIMARY LYMPHOSARCOMA OF THE LARYNX IN A CHILD

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A 4 7/12-year-old Caucasian female with a history of "croup-like symptoms" and persistent airway obstruction, was found to have a primary lymphosarcoma by biopsy at the time of laryngoscopy and bronchoscopy. No metastatic disease was found. After an induction course of vincristine, prednisone and local irradiation, she received CNS prophylaxis with intrathecal methotrexate and cranial irradiation. Maintenance therapy, administered over a 2¾ year period, consisted of cyclophosphamide, methotrexate, and 6-mercaptopurine. Excluding the diagnostic evaluation, she was hospitalized only once for the management of suspected sepsis, gastrointestinal ulceration and severe bone marrow depression. Since discontinuing treatment 27 months ago, she has remained free of disease.

Malignant tumors of the larynx in children are rare, and lymphosarcoma of the larynx in a young child has never been reported in the American literature. In general, sarcomas constitute only 1% of laryngeal neoplasms.[1] This paper reports on a 4½-year-old girl with lymphosarcoma of the larynx, presenting with symptoms of "croup," who was treated with irradiation and chemotherapy.

The first report of lymphosarcoma of the larynx was by McKenty[2] in 1934. Of four cases reported by Wang[3] one was a 14-month-old male with a reticulum cell sarcoma, who was treated with 3000 rads in 30 days with Co_{60}, and who had no evidence of disease after 8½ years. Dickson[1] reviewed the literature and added 2 cases of lymphosarcoma to the 14 previously reported. Anderson et al[4] added another case and stressed the need for complete medical workup, including thorough physical examination, complete blood count, serum uric acid level, liver and kidney function tests, bone marrow examination, liver and chest x-rays, lymphangiography and abdominal contrast radiography for staging of the lesion, after histological proof of the disease is obtained.

CASE REPORT

K.B. was referred to one of the authors (SRC) on November 28, 1972, with the chief complaint of noisy, difficult breathing. She was born on May 23, 1968, of a normal pregnancy and birth history. Her past history was noncontributory with no previous episodes

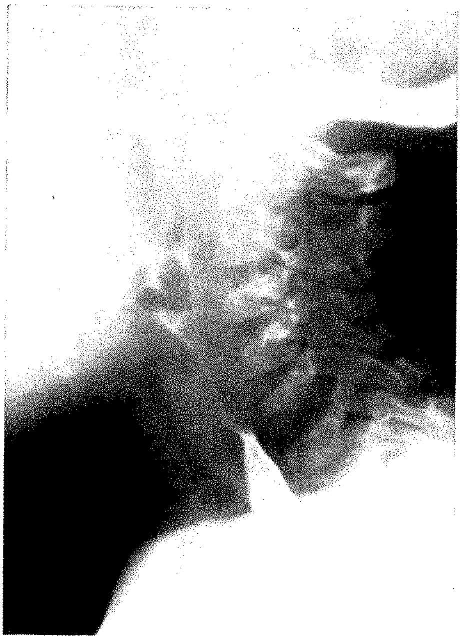
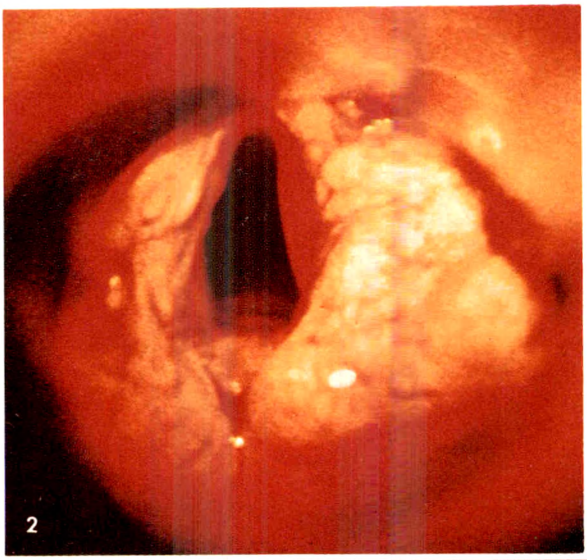
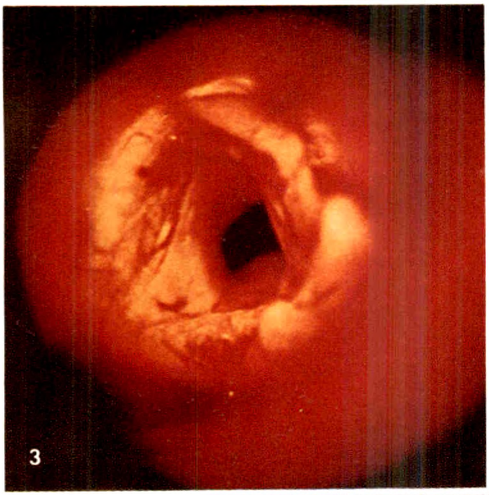
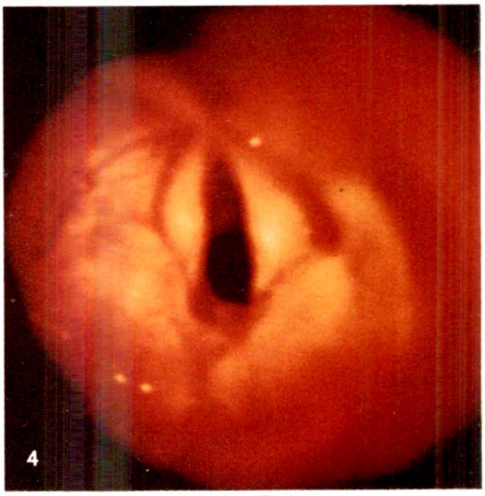


Fig. 1. Lateral roentgenogram of the airway taken with a barium swallow. The esophagus is normal but the airway is constricted by soft tissue mass in the larynx, trachea and periesophageal areas.







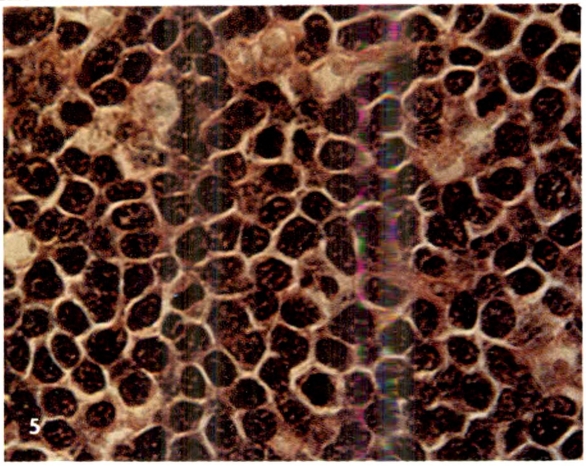


Fig. 2. Direct laryngoscopy shows grape-like lesions infiltrating the entire larynx in both supraglottic and subglottic areas.

Fig. 3. Laryngoscopy shows close-up view of the infiltrate in the subglottic space.

Fig. 4. Final direct laryngoscopy shows the normal larynx after chemotherapy and irradiation.

Fig. 5. Lymphocytic lymphoma, shows uniform population of small lymphoid cells with scant cytoplasm. Several mitotic figures are shown. (H & E X190)

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of laryngitis or "croup." One month prior to being seen she had been hospitalized elsewhere for the treatment of "croup" but failed to respond to the usual management and was discharged on antibiotics and bronchodilators. There were no known allergies and she failed to respond to the medication. The family history was of importance in that the patient's mother was under treatment for a Stage 4B Hodgkin's disease and that a cousin had had a Wilms' tumor.

Examination revealed a moderately distressed, pale, Caucasian female child with inspiratory and expiratory stridor. Her voice was very husky and her cough "barking." Indirect laryngoscopy revealed an edematous larynx with subglottic narrowing. The vocal cord mobility was found to be normal. The neck was free of masses and the thyroid was not palpable. She was admitted to CH LA for endoscopy and biopsy.

On November 29, 1972, direct laryngoscopy, bronchoscopy and biopsy of the laryngeal and upper tracheal tumor were accomplished. Preoperative blood count and urinalysis were reported as normal. Routine and fungal cultures were reported as normal. An x-ray of the chest preoperatively revealed no evidence of disease. A lateral film (Fig. 1) showed narrowing of the laryngeal and subglottic airway.

The direct laryngoscopy revealed the following findings (Fig. 2). Numerous, small, grape-like lesions were seen to arise from the anterior commissure, the supraglottic area, the right true and false cords, extending down into the immediate subglottic area through the anterior commissure. The subglottic area was narrowed remarkably by a horseshoe-shaped, irregular, grape-like mass similar to the laryngeal supraglottic abnormality (Fig. 3). A single knob-like projection from the posterior wall into the lumen was also noted. The numerous grape-like lesions were removed from the larynx and bronchoscopy was performed. The trachea was normal below the area of stenosis, and the bronchi were normal. To improve the airway, a large amount of the tumor mass was removed endoscopically. Esophagoscopy was performed and the esophagus and postcricoid area were found to be normal. The patient tolerated the procedure well, and her airway was remarkably improved. The biopsy revealed a malignant small-celled neoplasm, probably in the leukemia-malignant lymphoma group (Fig. 5). Following the biopsy, the complete medical workup revealed no evidence of a focus of tumor elsewhere.

Irradiation and chemotherapy were advised; and since the patient's mother was being treated at UCLA, she was transferred to that center for therapy.

On admission to UCLA, physical examination revealed a thick Caucasian female in no respiratory distress with mild inspiratory stridor. Her height was 105 cm (50th percentile), weight 16.2 kg (17th percentile), pulse 100/min and regular, blood pressure 110/60 supine, temperature 38.5 C. The remainder of the examination was completely normal except for the findings of rales at the right base and the inspiratory stridor. There was no organomegaly and no masses were palpable in the abdomen. The neurological examination was completely normal.

A right middle lobe infiltrate was present on an x-ray examination, and oral penicillin was given. Her hemogram was normal, and a lateral film of the neck showed the soft mass behind the trachea extending into the vallecula and constricting the subglottic area (Fig. 1). Spleen scan, cerebrospinal fluid examination, and a repeated bone marrow examination were entirely normal. After an initial dose of chemotherapy, she was discharged with plans for further treatment as an outpatient.

The patient was managed on the St. Jude's protocol then being used for the treatment of lymphoma. It consisted of three phases: induction of remission with consolidation, CNS prophylaxis and maintenance chemotherapy. The induction phase consisted of radiation to the tumor site, prednisone 40 mg/M^2/day po, and vincristine 1.5 mg/M^2/wk IV. When remission was achieved, consolidation was accomplished with a three-day course of 6-mercaptopurine 1.0 gm/M^2/day IV, followed by three days of methotrexate 10 mg/M^2/day IV. On the seventh day, the patient received a single dose of cyclophosphamide 600 mg/M^2 IV. Two weeks after the consolidation, CNS prophylaxis was begun. Rads to the cranium (2400) were administered over 2½ weeks concurrently with methotrexate 12 mg/M^2 twice a week, intrathecally, for five doses. Upon completion of the CNS prophylaxis, maintenance therapy was begun with 6-mercaptopurine 50 mg/M^2/day po, cyclophosphamide 200 mg/M^2/wk po, and methotrexate 20 mg/M^2/wk po. In addition, beginning 70 days after the first remission and every 12 weeks thereafter, a "reinduction" pulse was given which consisted of vincristine 1.5 mg/M^2/wk IV for three weeks and prednisone 40 mg/M^2/day po for 15 days. During maintenance therapy, the goal was to keep the WBC between 3,000 and 5,000.

Following discharge the patient received a total of 3500 rads to the larynx and neck: 2000 rads initially followed by 1500 rads one week later. She tolerated the radiation and induction chemotherapy well. Bone marrow aspiration in mid-January, 1973, was again negative for tumor cells. However, hypocellularity secondary to the chemotherapy was appreciated. Lateral neck films at this time showed complete resolution of the soft tissue swelling.

Following consolidation, she developed fever and oral ulcers. Her appetite deteriorated and she refused oral fluids. Therefore, she was admitted to UCLA for a second time on January 30.

Pertinent physical findings included a temperature of 40 C, small ulcerations on the buccal mucosa and lips, injected pharynx, grade 2/6 systolic ejection murmur, and anal ulcers with perianal erythema. She was not dehydrated clinically, and there had been no change in her weight since discharge six weeks previously.

Hemogram showed a hemoglobin of 7.2 gm/ml, WBC 200 with no neutrophils and a platelet count of 24,000. Blood and urine cultures obtained on admission were negative, but a throat culture grew B hemolytic streptococcus. Stools were guaiac negative.

Because of suspected sepsis, she was started on gentamicin 5 mg/kg/day IV, divided into q7h doses and cephalothin 150 mg/kg/day IV, divided into q6h doses. These were discontinued and replaced by penicillin-G 50,000 units/kg/day IV, divided into q6h doses. After 48 hours she became afebrile. Nevertheless, the penicillin was continued for a full ten days. Her hydration was maintained intravenously and her perianal inflammation treated with sitz baths. All antitumor chemotherapy was withheld. The oral and anal lesions healed, and her oral intake returned to normal. She was discharged after 12 days.

The hemogram just prior to discharge, following an infusion of one unit of packed red blood cells, showed a hemoglobin of 9 gm, with a WBC of 5,300 with 54% neutrophils and 8 bands. The platelet count was 120,000.

One week after discharge the CNS prophylaxis was begun and well-tolerated. Following completion of that phase of chemotherapy she was started on the maintenance phase. Subsequently the patient continued to do well without signs of significant toxicity from the chemotherapy.

Direct laryngoscopy in June, 1973, showed the larynx to be perfectly normal in every respect (Fig. 4). Chemotherapy was discontinued in October, 1975. The patient has been free of clinical disease for two years and nine months. Bone marrow and cerebrospinal fluid examination at the time the treatment was stopped were normal. She has been off medication now for 27 months and remains clinically free of disease.

DISCUSSION

This patient appears unique in that we have been able to find only one other reported case of lymphosarcoma of the larynx in a child.[3] Lymphosarcomas in general are uncommon in children, with overall incidence of 3.5-10% of all childhood tumors.[5-7] The term lymphosarcoma encompasses all the non-Hodgkin's tumors of lymphoid origin.

The age distribution in children suggests a bimodal occurrence with peaks at 5 and 12 years.[8,9] Seventy-five percent of these tumors originate in the peripheral lymph nodes, usually in the cervical region.[10,11] Other common sites in descending order include the mediastinum, abdomen, and pharynx. Pharyngeal involvement, presenting as an enlarging mass, accounts for less than 10% of cases.

Current efforts at therapy are directed not only at the primary tumor, but also towards the prevention of conversion to acute lymphocytic leukemia and central nervous system involvement. Prior to 1968, leukemic transformation occurred in up to 50% of reported cases,[12] but with more agressive protocols, such as that used in our patient, the conversion rate appears to be decreasing.[12,13] Clinical central nervous system involvement was uncommon prior to effective systemic treatment.[14,15] However, recent data show that, with improved systemic regimens without CNS prophylaxis, meningeal relapse is an important cause of treatment failure.[6]

The overall five year survival rate reported for children with non-Hodgkin's lymphoma prior to 1963 was 9%.[13] Cell type and location of the primary tumor were not significant variables. More recently, multidisciplinary treatment has resulted in survivals of 44 to 51%.[13,17,18] In these series, staging according to the Ann Arbor classification is an important factor, with the above survival figures representing Stages I and II.[19]

Our patient's course confirms the necessity for an aggressive approach to diagnosis and treatment. Evaluation should include hemogram, urinalysis, chest roentgenogram, lumbar puncture, bone marrow aspiration, liver-spleen scan, intravenous pyelogram, and bone survey. New protocols using even more aggressive chemotherapeutic agents and irradiation, with CNS prophylaxis, are under evaluation and will, hopefully, improve the prognosis for patients with these tumors.

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ADDENDUM

The patient was seen again at UCLA on June 26, 1978 following a bump on the head, and was found to have a 5 x 5 cm right frontal parietal mass. An excisional biopsy revealed a low grade fibrosarcoma or fibrous histiocytoma, but the final diagnosis will depend on her future course.

EPIDERMOLYSIS BULLOSA ASSOCIATED WITH LARYNGEAL STENOSIS

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A boy with epidermolysis bullosa developed progressive laryngeal obstruction after age six months, with tracheotomy necessary at age three years. By eight years, the larynx was completely occluded by web and scar. Stenosis recurred repeatedly over the next seven years, three to six months after each corrective procedure, but laryngeal patency has been better-maintained since age 15. Laryngeal stenosis, presumably secondary to epithelial detachment, although a rare complication of epidermolysis bullosa, can be serious and life-threatening.

Skin lesions are of importance to the otolaryngologist because many dermatological problems have representations in the ear, nose, and throat, esophagus, and tracheobronchial tree. Cutaneous hemangiomata, café au lait spots, neurofibromata or papillomata (skin and venereal), for example, may indicate the presence of otolaryngologic disease. This report of a laryngeal stenosis, a problem not heretofore reported in the hereditary skin disease epidermolysis bullosa, hence seems appropriate.

Epidermolysis bullosa is a hereditary disease of the skin, best known to otolaryngologists because of dysphagia from involvement of the esophagus with stricture formation (Fig. 1). There have been no reports of laryngeal involvement in epidermolysis bullosa in the American literature, although involvement of the oropharynx and bronchial tree have been reported.[1]

Epidermolysis bullosa was first reported by Fox in 1879.[2] Schild et al report and give historical evidence of esophageal involvement by this disease.[3] As of 1974,[4] approximately 50 cases of esophageal stricture in epidermolysis bullosa had been reported. No mention has been made of laryngeal involvement by the disease (epidermolysis bullosa) and in treating strictures under general anesthesia, no mention has been made of postintubation reactions or sequellae in the larynx or trachea. Three cases of stricture of the esophagus associated with this disease have been seen at CHLA, but the patient reported here is the only known instance of severe and prolonged chronic laryngeal stenosis in epidermolysis bullosa.

DISCUSSION OF THE DISEASE

Epidermolysis bullosa is a rare hereditary skin disorder characterized by the formation of vesicles, bullae and ulceration following mechanical trauma (Fig. 3). The bullae break and heal with scarring. The dystrophic form is associated with mutilating contractures of

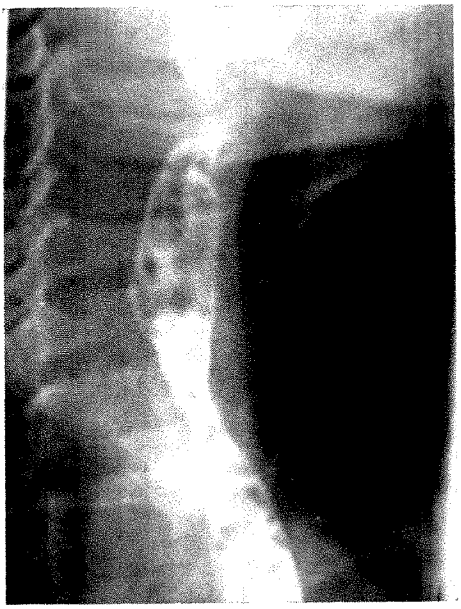


Fig. 1. Lateral x-ray showing stricture of esophagus.

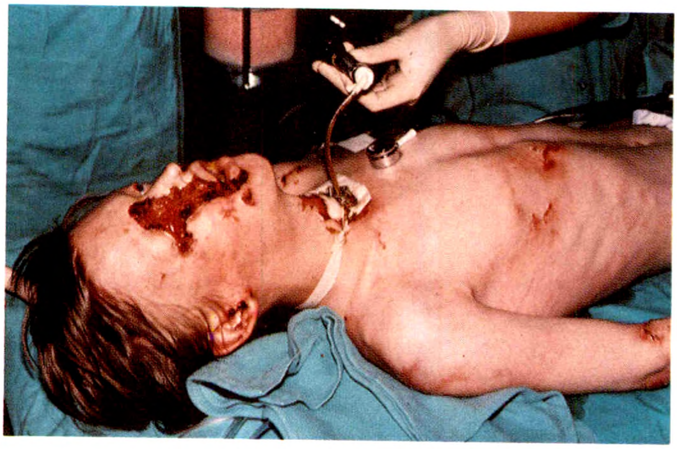


Fig. 2. Severe ulcerations of face, neck, chest and extremities which bleed easily. The tracheotomy site ulceration is seen.

fingers, webbing, loss of nails, and bony changes. Approximately one third of those affected die in early childhood, usually from complicating infection.

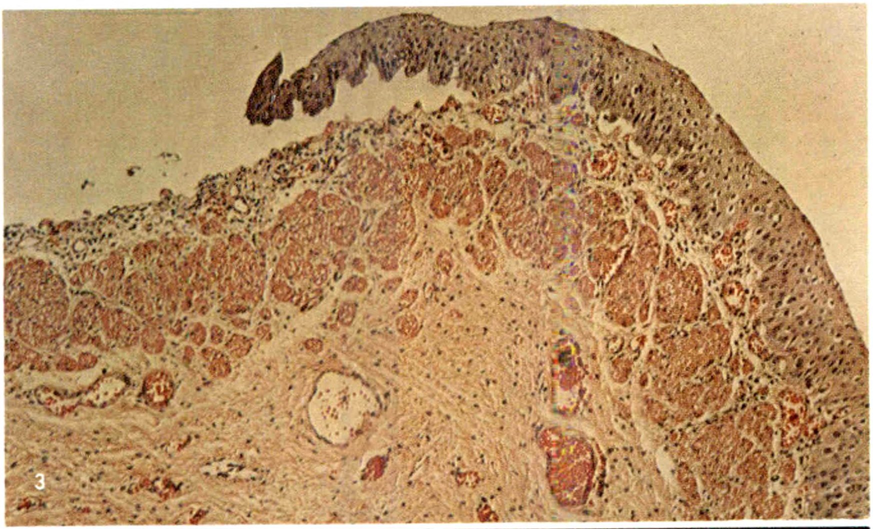
For details of electron microscopy and light microscopy of skin lesions the reader is referred to Pearson et al.[5] There is only one autopsy report of findings in the larynx,[5] showing squamous metaplasia and invasion of upper layers of the epidermis by monilial filaments.

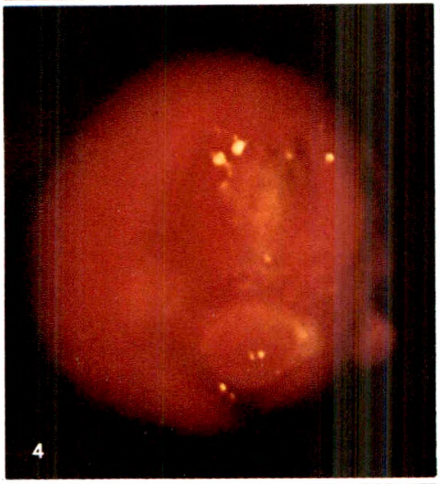
CASE REPORT

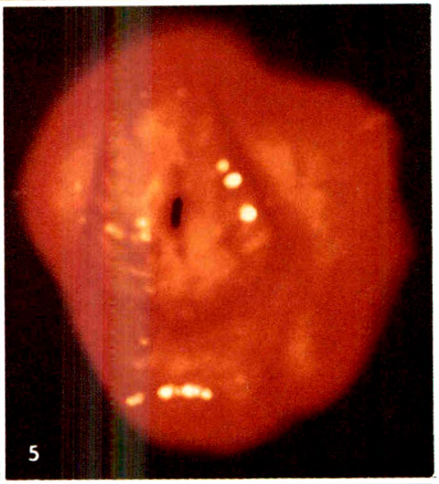
M.M., an eight-year-old male, was first seen by us on July 31, 1970. One of three siblings, he was noted at age three days to have findings typical of epidermolysis bullosa. Other than problems with skin lesions, he was well until six months of age. He then began to have respiratory difficulty, with loss of "vocal power," and with each cold, developed increasing respiratory obstruction. The respiratory distress and loss of voice progressed and at three years of age he was noted to be very stridorous. On May 28, 1965, severe distress from airway obstruction resulted in his hospitalization elsewhere. He was given symptomatic treatment, but airway obstruction increased, and a tracheotomy was performed on May 29, 1965. Postoperatively, he did well, and was discharged on June 8, 1965. Direct laryngoscopy was performed after endotracheal anesthesia and tracheotomy had been performed, and the larynx was reported as normal except for subglottic edema.

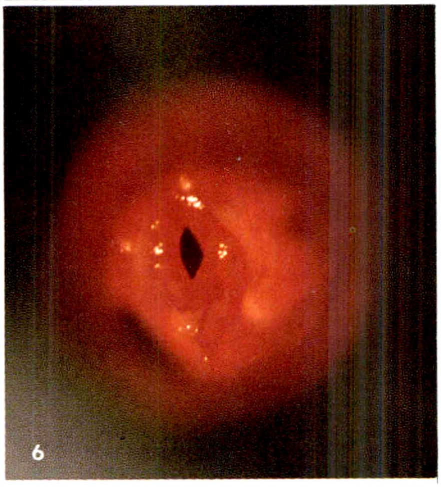
Since his tracheotomy he had had no laryngeal treatment. His tracheotomy tube was periodically changed, and his voice became progressively poorer until it was completely lost. On July 31, 1970, examination showed severe ulceration of face, neck, chest (Fig. 2), and extremities, and the hands showed scarring and defective nails and digits. Ear canals and nasal vestibulae were ulcerated. Oral lesions were also present, and he had a buccoesophageal voice. Occlusion of the tracheotomy tube showed the larynx to be completely blocked. Indirect laryngoscopy revealed a complete closure of the larynx at the cordal level and the right arytenoid was dislocated medially; no orifice could be identified. Since the patient was on steroid treatment, he was hospitalized at CHLA. Laryngoscopy was performed on November 30, 1970.

Direct laryngoscopy showed the larynx to be closed by a web at the cordal level, with a posterior scar band in the interarytenoid area (Fig. 4). The web was incised and the larynx dilated and he was discharged on the day of surgery. Five days later his voice was good, and the airway was improved (Fig. 5). Within three months the larynx again









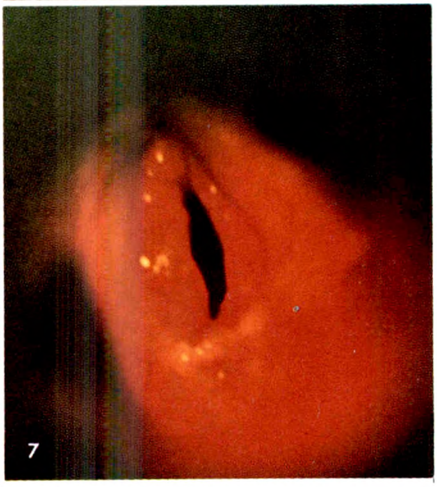


Fig. 3. Esophageal lesion showing subepithelial vesicles (bulla formation), and ulceration with inflammation. (H & E X32)

Fig. 4. View of larynx showing complete closure at vocal cord level by web with thick interarytenoid scar.

Fig. 5. View of larynx after multiple procedures. The interarytenoid scar is still present. The airway is patent.

Fig. 6. The larynx after incision of the web.

Fig. 7. Increased glottic chink after multiple incisions.

closed, and he subsequently required numerous procedures at three to six month intervals to correct the recurrent stenosis. Stenting was attempted but severe reaction in the skin of the neck resulted.

From April until November, 1977, his larynx remained patent, but closed to one third normal (Fig. 6). On November 16, 1977, another procedure was performed, and the tracheotomy tube size was reduced. Since for the past year the laryngeal opening has been adequate, it is planned to decannulate him soon (Fig. 7). His skin lesions still are troublesome, but otherwise he functions well.

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NEUROFIBROMA OF THE LARYNX IN A CHILD

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Laryngeal obstruction due to neurofibromatosis in a girl with von Recklinghausen's disease first occurred in the neonatal period, and recurred by age seven years. She has done well for four years following laryngofissure surgery. Pharyngeal and laryngeal neurofibromatosis are rare manifestations of von Recklinghausen's disease. The dominant hereditary pattern of this disease requires that the condition be considered when respiratory distress occurs in the child of an affected parent, whether or not skin tumors or other features are present.

Neurogenic tumors of the larynx are uncommon, and very rare in infancy. This paper reports on a child who had had a neurofibroma removed from the neck, at another hospital, in the neonatal period, and who could not be decannulated because of a similar tumor in the larynx.

HISTORY

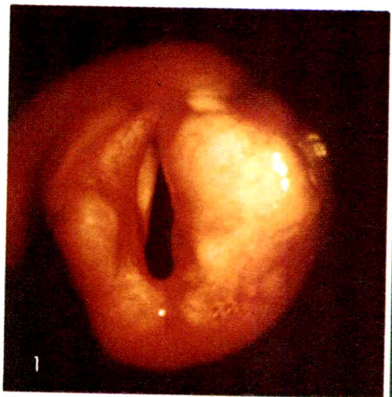
Generalized neurofibromatosis, or von Recklinghausen's disease, is not uncommon. First described by von Recklinghausen in 1882, it is usually a familial disease, occurring in approximately 1 in 3,000 births (Crowe et al).[1] A laryngeal lesion was first described by Suchanek in 1925.[2] Cummings et al[3] reviewed the world literature up to 1961, and stated that 77 neurogenic laryngeal tumors had been reported. Eleven were neurofibromas associated with von Recklinghausen's disease. The youngest patient was a 16-year-old. Seven hundred twenty-two benign laryngeal lesions were reviewed by New and Erich,[4] who found only one neurofibroma. (Holinger and Cohen[5] reported a single patient with neurofibroma.) In their review of 1,197 benign tumors of the larynx, Van Loon and Diamond[6] reported only one neurofibroma. Gibbs et al[7] reported an infant three months of age with laryngeal and tracheal neurofibroma, and Smith,[8] three cases of solitary laryngeal neurofibroma, two in six-year-old males, one removed by the lateral neck approach and the other by laryngofissure.

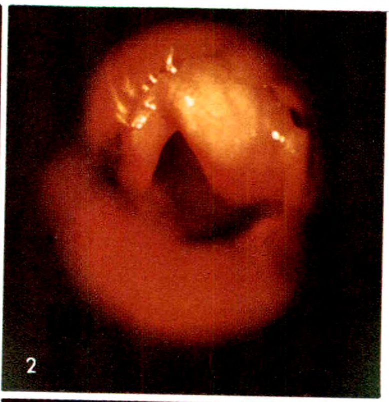
The diagnosis may be made by direct laryngoscopy and biopsy. The lesion most often occurs in the supraglottic larynx, is submucosal, and produces dysphonia and airway obstruction. A smooth mass lesion of this type which is slowly progressive, especially with a family history of neurofibromatosis, should alert the laryngologist to the probable diagnosis.

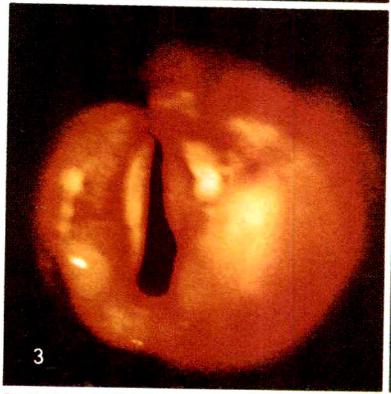
CASE REPORT

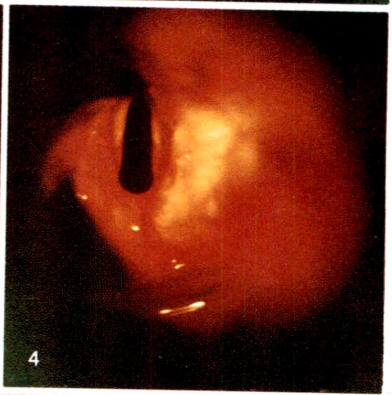
R.S., born on November 13, 1967, was first admitted to CHLA on July 28, 1971. Her history was that of having respiratory difficulty with cyanosis, and with a tumor mass noted in the right side neck soon after her birth. (The mother had von Recklinghausen's disease but two other siblings were normal). She was hospitalized in another hospital, where a large neurofibroma was removed from the hypopharynx and larynx through a lateral pharyngotomy approach. A tracheotomy and gastrostomy were performed. Following surgery she required hospitalization for 18 months. She eventually had her gastrostomy tube removed but still required the tracheotomy.

On admission to CHLA she was a well-developed, well-nourished Caucasian female, 3½ years of age, who wore a tracheotomy tube. Her voice was husky and her airway through the larynx was only fair. Multiple café au lait spots were noted, but no skin tumors were found. There was a healed right neck









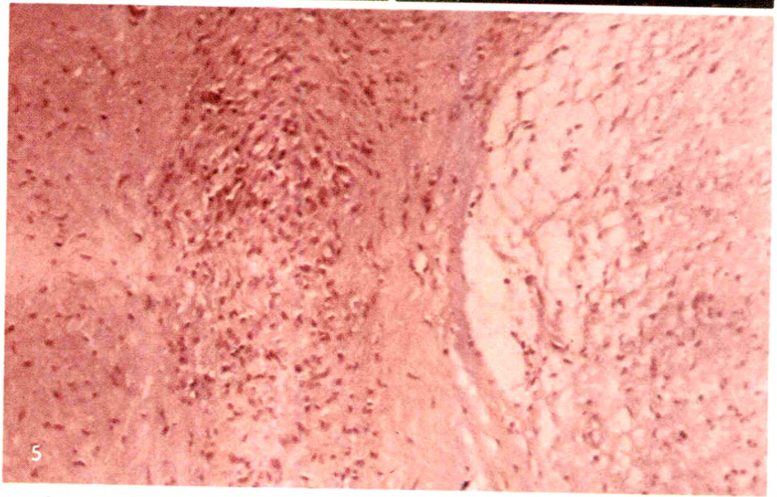


Fig. 1. Laryngoscopic view shows the smooth mass filling the right ventricular band obliterating the ventricle.

Fig. 2. View of epiglottis shows infiltration on the right side due to neurofibroma invasion.

Fig. 3. View of postoperative larynx immediately following removal of neurofibroma through a laryngofissure.

Fig. 4. Three-month postoperative view of the larynx.

Fig. 5. Neurofibroma of larynx, showing hyperplastic nerve with thick fibrous sheath and adjacent myxoid (Anton's type B) tissue. (H & E X75)

scar and a gastrostomy scar. She was alert, active and in no distress. An x-ray of the chest was normal and the blood count and urinalysis were normal.

Direct laryngoscopy and bronchoscopy under general anesthesia were performed. The procedures revealed the following findings: the base of the tongue, epiglottis, arytenoid and aryepiglottic folds were normal. There was fullness of the right false cord by a smooth tumor mass obliterating the ventricle (Fig. 1). The right vocal cord remained in the midline and did not move on abduction or adduction. The tracheobronchial tree was found to show inflammatory changes and mucopurulent secretion. The tracheotomy tube was changed and her infection was treated with antibiotics. Esophagoscopy performed at this time revealed narrowing of the pharynx and indentation of the right piriform sinus. The esophagus was normal.

The patient was seen four times over the next nine months and on April 17, 1972 she was decannulated. On May 18, 1972 she was again seen because of increasing respiratory difficulty particularly at night, and she was hospitalized. On June 5, 1972 the tracheotomy was replaced.

Repeated laryngoscopies revealed progressive enlargement of the laryngeal lesion but because she could tolerate plugging of the tracheotomy tube she was decannulated on March 6, 1974 only to return with fever and respiratory obstruction. The tracheotomy cannula was reinstated on March 12, 1974.

Complete pediatric workup revealed a child with complaints of dizziness and headaches and a functional heart murmur. Chest x-ray, skull x-ray, brain scan, electroencephalogram, barium enema and upper gastrointestinal x-rays, and IVP were all reported as normal.

On July 3, 1974 direct laryngoscopy and bronchoscopy were again performed. The laryngeal findings were those of supraglottic mass, smooth and submucosal, filling the right side of the larynx and arytenoid area. Again the right side of the larynx was fixed. The epiglottis was also infiltrated (Fig. 2). Laryngofissure surgery was performed on July 18, 1974. Using surgical microscopy, the plexiform neurofibroma was dissected and removed by following the tumor into the aryepiglottic folds, epiglottis, and base of the tongue (Fig. 5). Following closure, direct laryngoscopy revealed good patency of the larynx, and for the first time the right true cord could be well visualized (Fig. 3).

The postoperative period was uneventful and she was discharged on the ninth postoperative day. On October 7, 1974 she was decannulated (Fig. 4) but the tracheocutaneous fistula was not closed until July 2, 1976 because of her mother's fears that she would again need tracheotomy. Follow-up reveals a good airway, and she has had no problems to this time.

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- *Haemophilus influenzae*
- *Neisseria catarrhalis*

Note—Most strains of enterococci *(S. faecalis)* and a few strains of staphylococci are resistant to Keflex. It is not active against most strains of *Enterobacter* sp., *P. morganii*, and *P. vulgaris*. It has no activity against *Pseudomonas* or *Herellea* species. When tested by in vitro methods, staphylococci exhibit cross-resistance between Keflex and methicillin-type antibiotics.

Indications: Keflex is indicated for the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

- Respiratory tract infections caused by *S. pneumoniae* and group A beta-hemolytic streptococci (Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. Keflex is generally effective in the eradication of streptococci from the nasopharynx; however, substantial data establishing the efficacy of Keflex in the subsequent prevention of rheumatic fever are not available at present.)
- Otitis media due to *S. pneumoniae*, *H. influenzae*, staphylococci, streptococci, and *N. catarrhalis*
- Skin and soft-tissue infections caused by staphylococci and/or streptococci
- Bone infections caused by staphylococci and/or *P. mirabilis*
- Genitourinary tract infections, including acute prostatitis, caused by *E. coli*, *P. mirabilis*, and *Klebsiella* sp.

Note—Culture and susceptibility tests should be initiated prior to and during therapy. Renal function studies should be performed when indicated.

Contraindication: Keflex is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings: BEFORE CEPHALEXIN THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS AND PENICILLIN. CEPHALOSPORIN C DERIVATIVES SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS.

SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

There is some clinical and laboratory evidence of partial cross-allergenicity of the penicillins and the cephalosporins. Patients have been reported to have had severe reactions (including anaphylaxis) to both drugs.

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously. No exception should be made with regard to Keflex.

Usage in Pregnancy—Safety of this product for use during pregnancy has not been established.

Precautions: Patients should be followed carefully so that any side effects or unusual manifestations of drug idiosyncrasy may be detected. If an allergic reaction to Keflex occurs, the drug should be discontinued and the patient treated with the usual agents (e.g., epinephrine or other pressor amines, antihistamines, or corticosteroids).

Prolonged use of Keflex may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs test may be due to the drug.

Keflex should be administered with caution in the presence of markedly impaired renal function. Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

As a result of administration of Keflex, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP, Lilly).

Adverse Reactions: *Gastrointestinal*—The most frequent side effect has been diarrhea. It was very rarely severe enough to warrant cessation of therapy. Nausea, vomiting, dyspepsia, and abdominal pain have also occurred.

Hypersensitivity—Allergies (in the form of rash, urticaria, and angioedema) have been observed. These reactions usually subsided upon discontinuation of the drug. Anaphylaxis has also been reported.

Other reactions have included genital and anal pruritus, genital moniliasis, vaginitis and vaginal discharge, dizziness, fatigue, and headache. Eosinophilia, neutropenia, and slight elevations in SGOT and SGPT have been reported.

Administration and Dosage: Keflex is administered orally.

Adults—The adult dosage ranges from 1 to 4 gm daily in divided doses. The usual adult dose is 250 mg every six hours. For more severe infections or those caused by less susceptible organisms, larger doses may be needed. If daily doses of Keflex greater than 4 gm are required, parenteral cephalosporins, in appropriate doses, should be considered.

Children—The usual recommended daily dosage for children is 25 to 50 mg per kg divided into four doses.

Child's Weight	Keflex Suspension 125 mg/5 ml
10 kg (22 lb)	½ to 1 tsp q i d
20 kg (44 lb)	1 to 2 tsp q i d
40 kg (88 lb)	2 to 4 tsp q i d
Child's Weight	250 mg/5 ml
10 kg (22 lb)	¼ to ½ tsp q i d
20 kg (44 lb)	½ to 1 tsp q i d
40 kg (88 lb)	1 to 2 tsp q i d

In severe infections, the dosage may be doubled.

In the therapy of otitis media, clinical studies have shown that a dosage of 75 to 100 mg per kg per day in four divided doses is required.

In the treatment of beta-hemolytic streptococcal infections, a therapeutic dosage of Keflex should be administered for at least ten days.

How Supplied: For Oral Suspension, Keflex® (Cephalexin for Oral Suspension, NF), 125 mg per 5-ml teaspoonful, in 60, 100, and 200-ml-size packages and in Identi-Dose® (unit dose medication, Lilly) in packages of 100; 250 mg per 5-ml teaspoonful, in 100 and 200-ml-size packages and in Identi-Dose in packages of 100.

For Pediatric Drops, Keflex® (Cephalexin for Oral Suspension, NF), 100 mg per ml (5 mg per drop), in 10-ml-size packages, with dropper calibrated at 25 and 50 mg.

Pulvules® Keflex® (Cephalexin Capsules, USP), 250 or 500 mg, in bottles of 24 and 100 and in Identi-Dose in boxes of 100.

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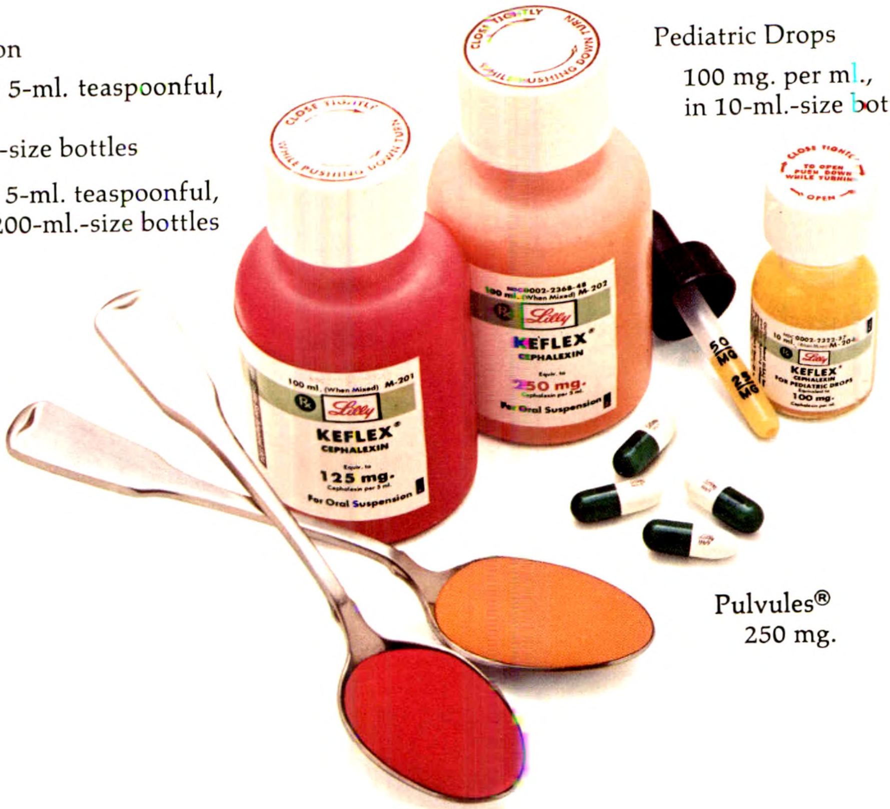

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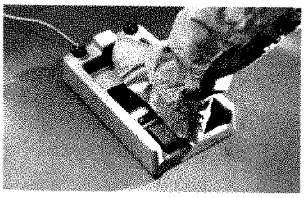

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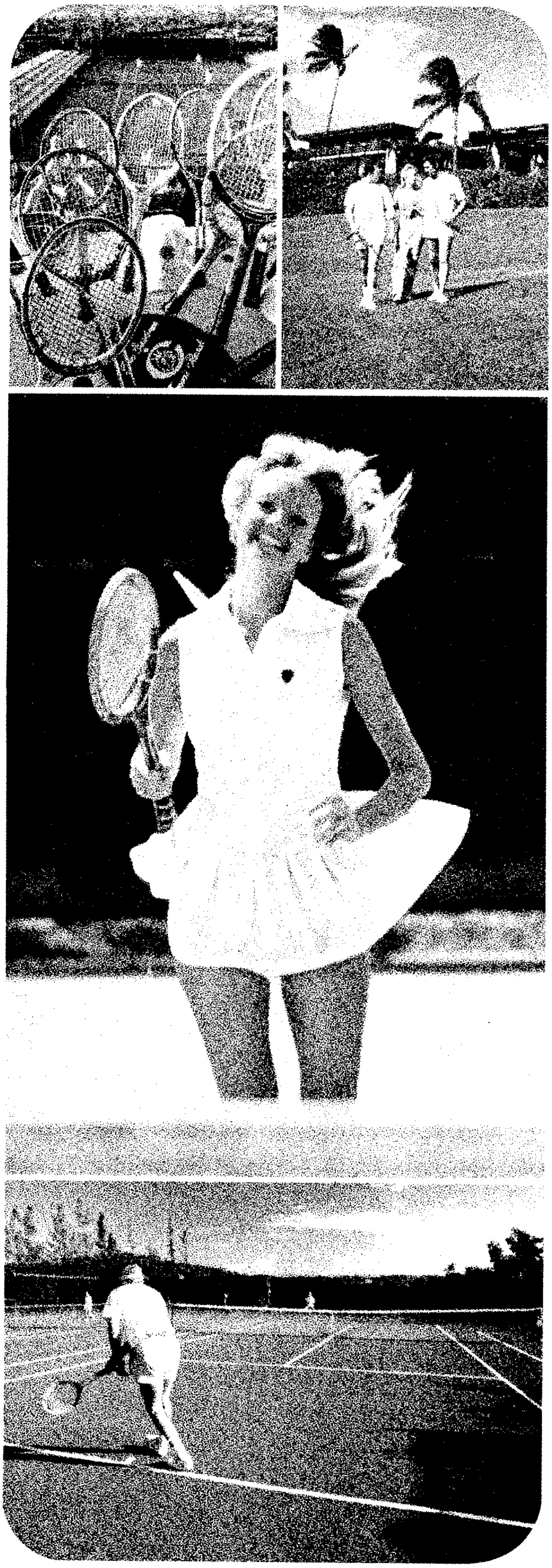

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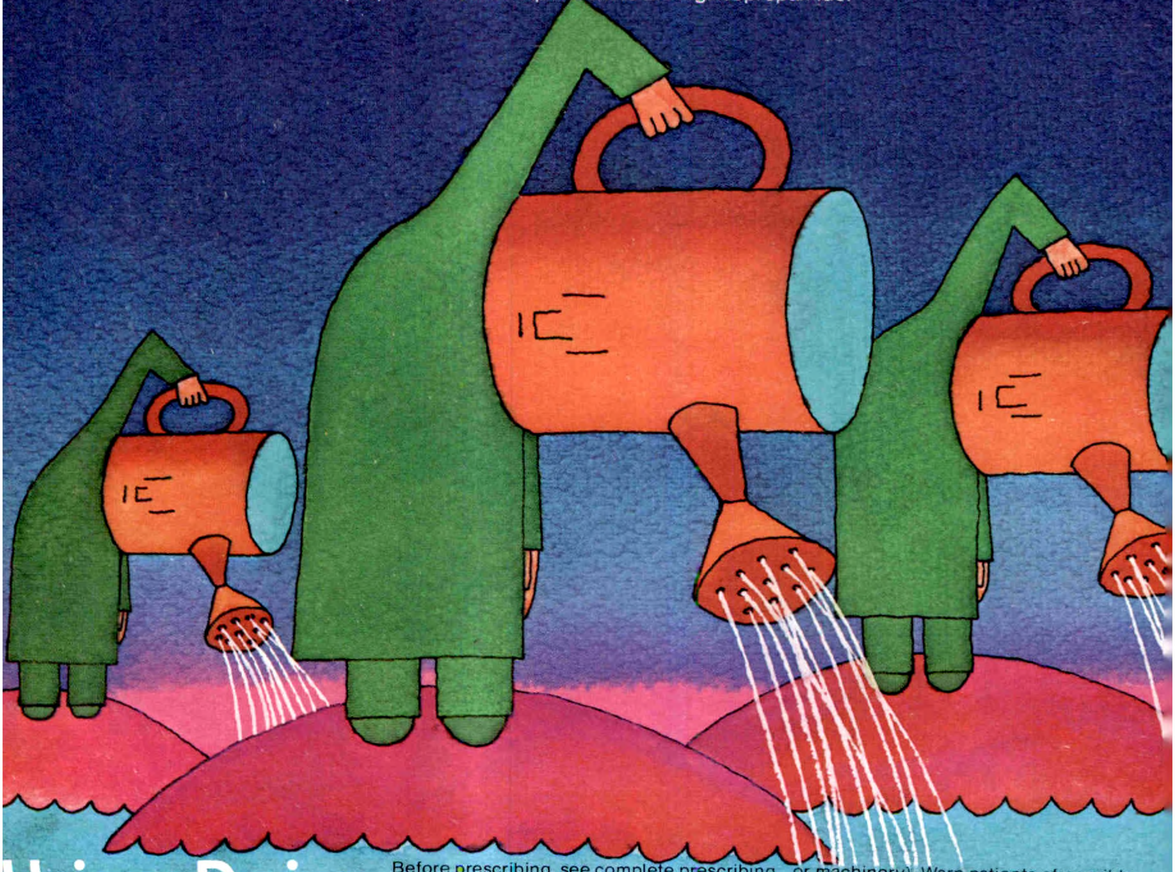

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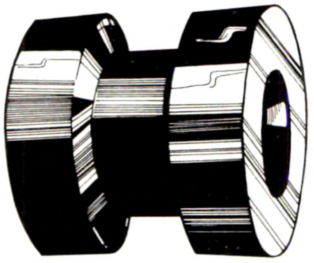

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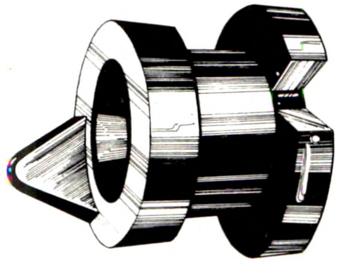

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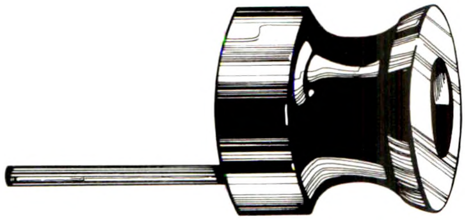

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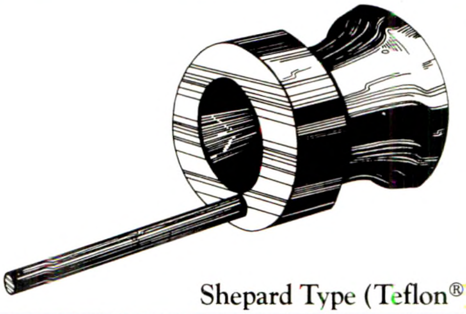

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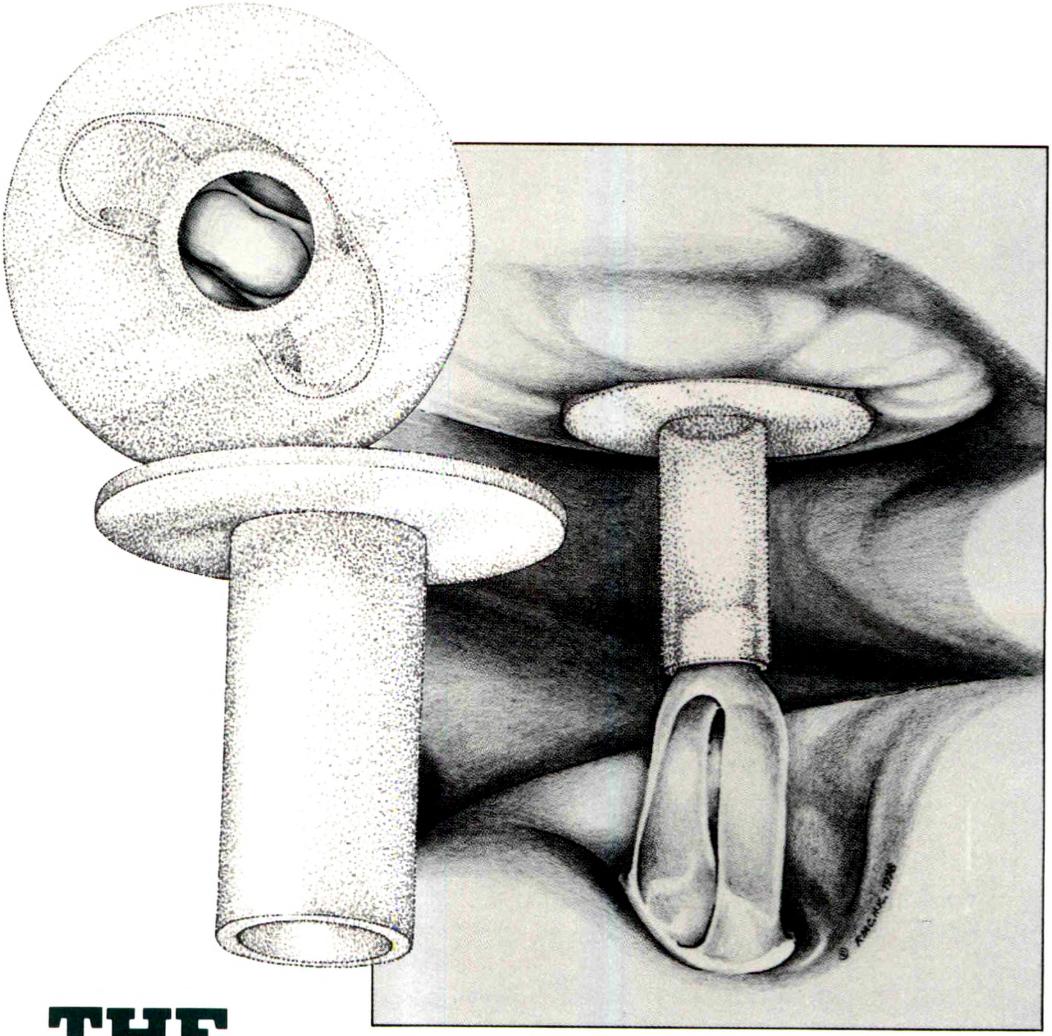

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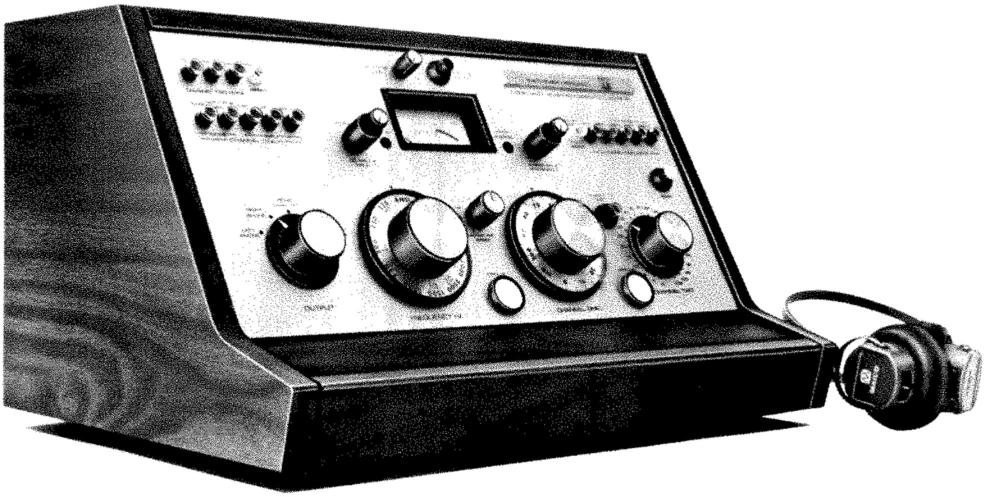

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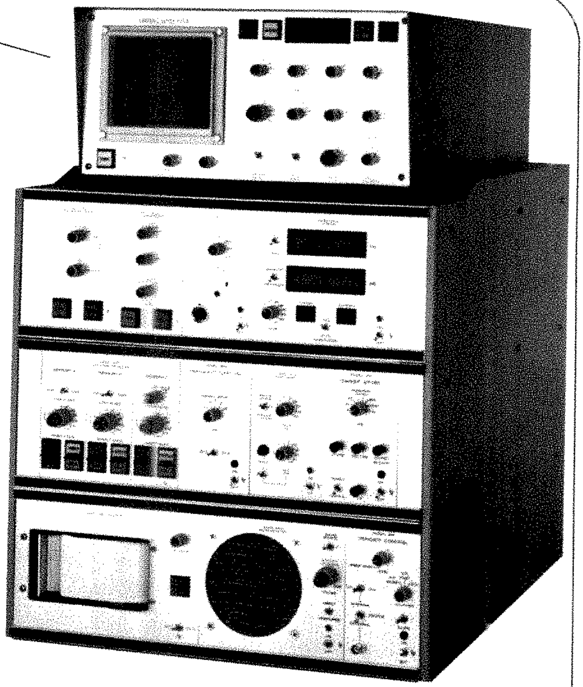

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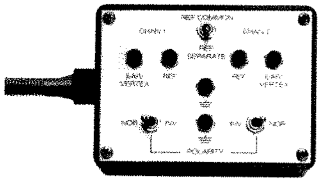

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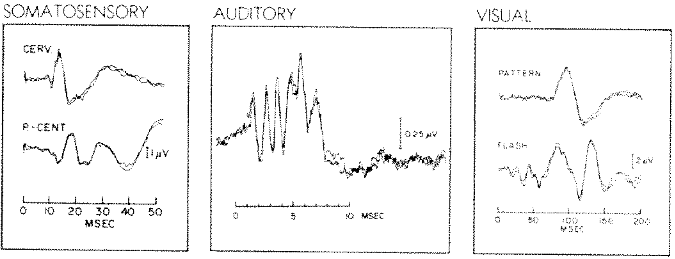
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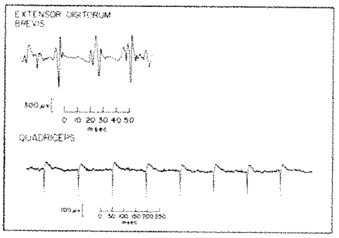

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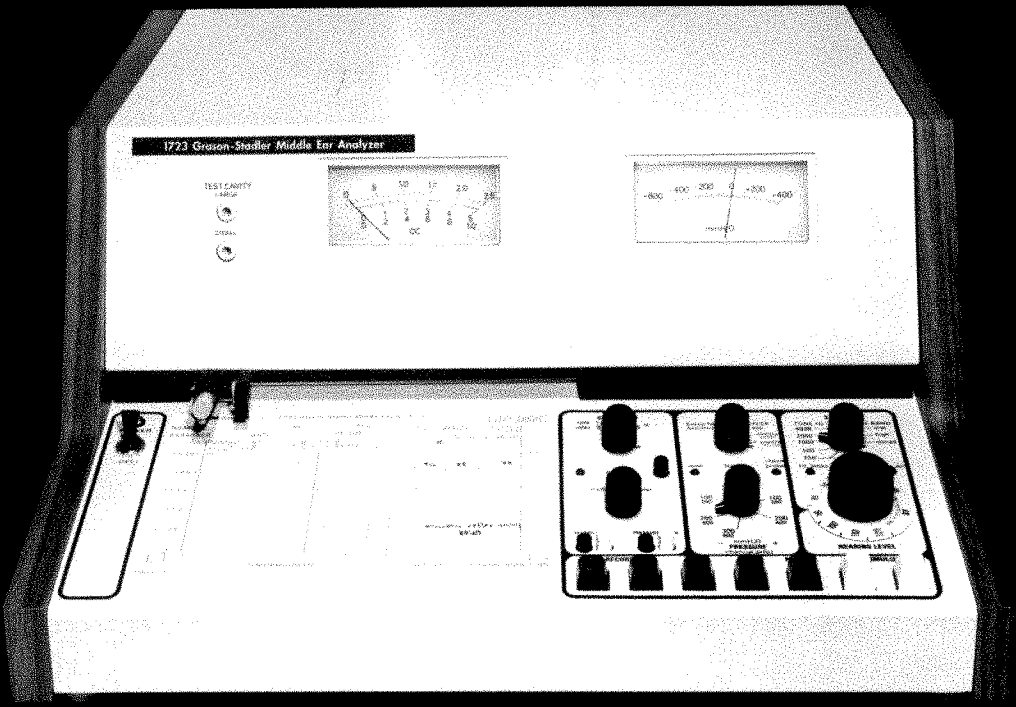

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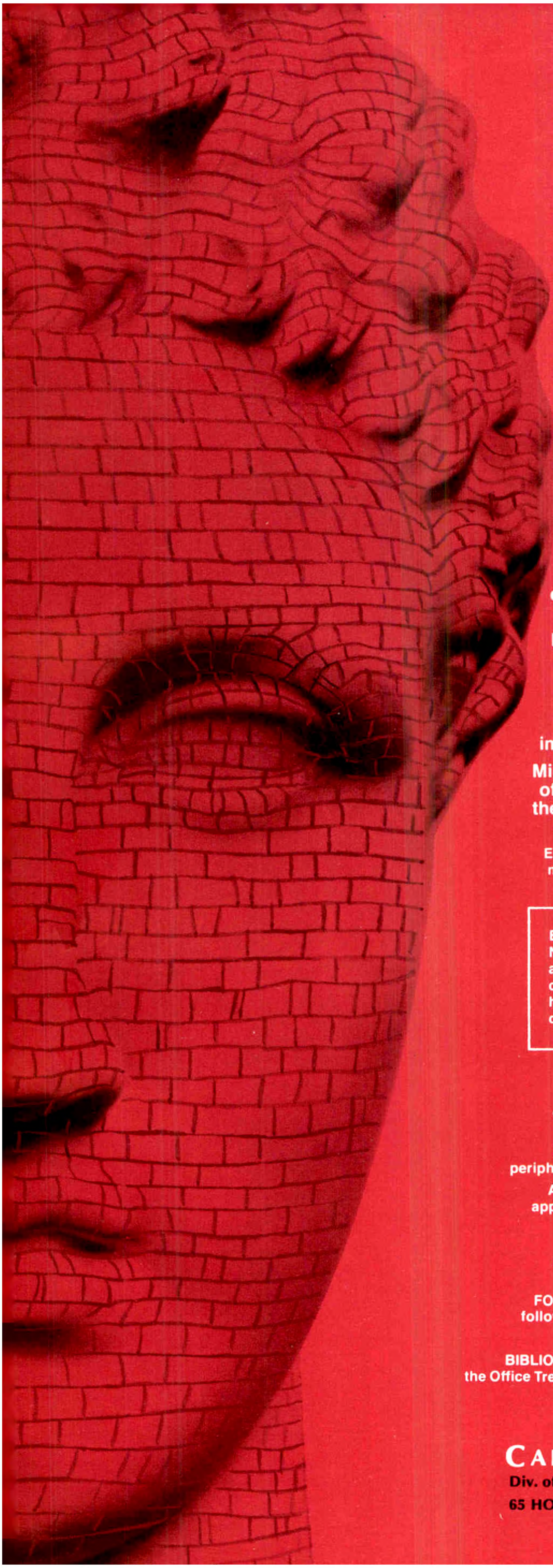

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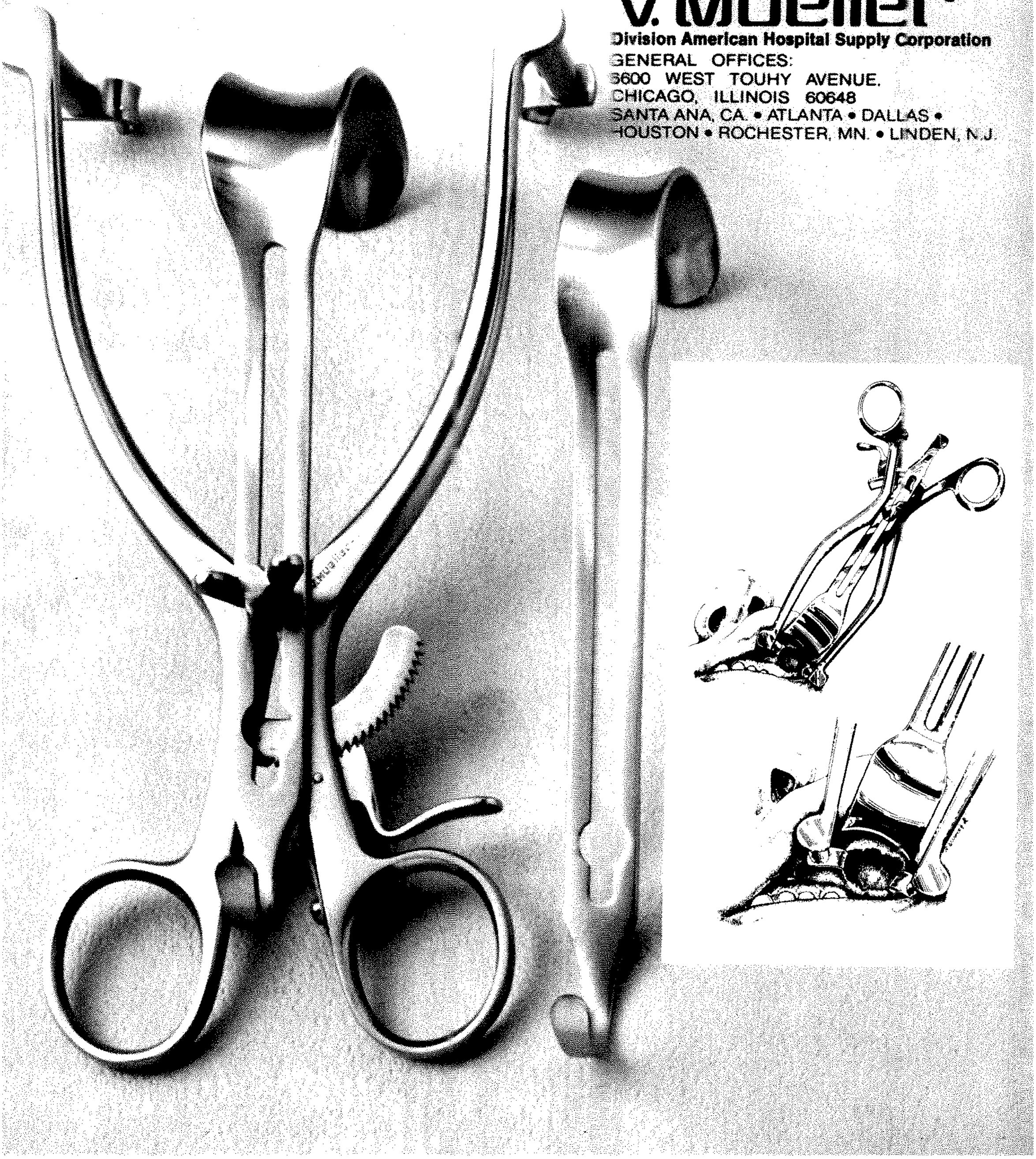

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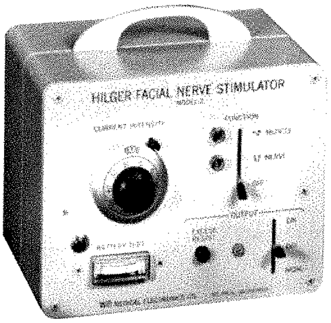

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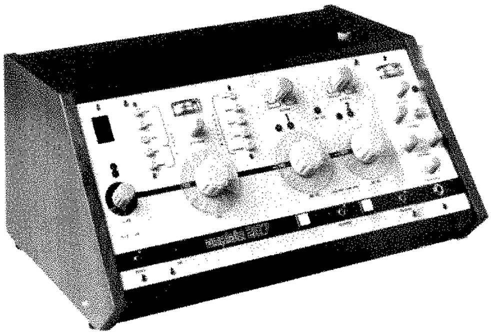

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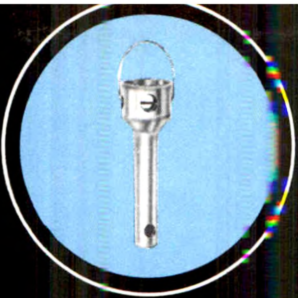

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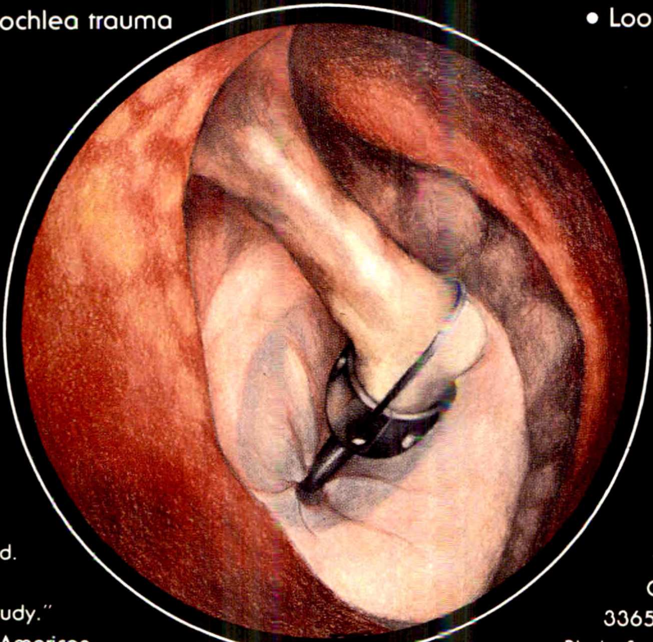

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DELAYED ENDOLYMPHATIC HYDROPS

HAROLD F. SCHUKNECHT, MD

BOSTON, MASSACHUSETTS

Delayed endolymphatic hydrops is a disease entity that can be differentiated from Ménière's disease. Typically it occurs in patients who have sustained a profound hearing loss in one ear, usually from infection or trauma, and then after a prolonged period of time develop either episodic vertigo from the same ear (ipsilateral delayed endolymphatic hydrops) or fluctuating hearing loss, also sometimes with episodic vertigo, in the opposite ear (contralateral delayed endolymphatic hydrops). The ipsilateral form of the disease may be treated by labyrinthectomy but no satisfactory therapy is available for the contralateral form of the disease.

The purpose of this paper is to describe the clinical manifestations of delayed endolymphatic hydrops, an entity which can be differentiated from Ménière's disease. The ipsilateral type of this disorder was described by Nadol et al[1] and by Wolfson and Leiberman[2] in almost simultaneous publications. It is characterized by the delayed onset of episodic vertigo of the Ménière's type caused by ears having preexisting profound hearing losses. Ménière's type vertigo may be defined as attacks of spinning type vertigo of sudden onset and prolonged duration (one or more hours), and of sufficient severity to cause nausea and vomiting. Most patients with this disorder retain normal hearing and vestibular function in their opposite ears, however it may also occur in patients with bilateral profound hearing losses. The contralateral type of delayed endolymphatic hydrops also occurs in patients who have had a profound unilateral hearing loss, but differs from the ipsilateral type in that they subsequently develop fluctuating hearing loss in the opposite ear, also occasionally with vertigo.

IPSILATERAL DELAYED ENDOLYMPHATIC HYDROPS

Twelve patients have been encountered who satisfy the criteria for the ipsilateral delayed hydrops syndrome (Table 1). Seven of these were previously reported by Nadol et al.[1] The criteria for inclusion in the group are: 1) profound hearing loss in one or both ears discovered incidentally in childhood or related to some specific disease or trauma, and 2) subsequent onset of episodic vertigo of the Ménière's type. Hearing losses were unilateral in ten and bilateral in two and equally distributed between right and left ears. The hearing losses were discovered incidentally in childhood in six, and were believed to be caused by head trauma in two, viral labyrinthitis or upper respiratory infection in two, mumps in one and influenza in one. Table 2 shows a tabulation of alleged causes of unilateral deafness in the cases reported to date. The time span from the discovery of deafness to the onset of episodic vertigo was one year for the patient having mumps and two years for one of the patients in which the etiology of the hydrops was head blow. Although the head blows were severe there was no clear history of skull fracture and it is not known whether radiologic studies were done. In the remaining ten patients the time spans ranged from 11 to 45 years with an average of 25.8 years.

Two of the patients had spontaneous subsidence of episodic vertigo, one after four years and another after one year

---

From the Harvard Medical School and the Massachusetts Eye and Ear Infirmary, Boston, Massachusetts.

Presented at the meeting of the American Otological Society, Inc., Palm Beach, Florida, April 23-24, 1978.

TABLE 1. IPSILATERAL DELAYED ENDOLYMPHATIC HYDROPS

Early History			Late History					
	Profound Hearing Loss	Age	Onset of Episodic Vertigo	At Age	Caloric Responses Right	Caloric Responses Left	Labyrinthectomy Year	Labyrinthectomy Age
1 CE*	L	6 - mumps	+	7	N	N	1966-L	10
2 LP	R	9 - flu	+	53	DVR	N		
3 CW*	L	8 - trauma	+	10	N	DVR	1970-R	22
4 RD*	L	4 - trauma	+	27	N	N	1973-L	27
5 JC	R	Childhood	+	18	N	N	1976-R	21
6 A La	R	Childhood	+	16-20	DVR	N		
7 A Lo*	R	Childhood	+	42	0	N	1966-R	42
8 McN*	L	Childhood	+	25	N	DVR	1970-L	28
9 FS	R	Childhood	+	25-26	DVR	N		
10 CD*	L	Childhood	+	32	N	DVR	1964-L	34
11 RM	Bilat.	Childhood	+	33	DVR	N		
12 VV*	Bilat.	Childhood	+	48	0	N	1973-R	51

*Previously reported by Nadol et al.
DVR - Decreased vestibular response. R - Right; L - Left; N - Normal.

of symptoms. At the time of the original examination, the remaining ten had experienced episodic vertigo for periods of time ranging from less than 1 year to 14 years with an average of about 3½ years.

Caloric tests were performed by the Kobrak minimal technique using 5 cc of water at 26.6 C and, if no response occurred, with 5 cc of ice water. By this method the responses were judged to be normal in the opposite ears of all ten patients with unilateral hearing loss. The deaf ears in this group showed normal responses in three, decreased vestibular responses in six, and no response in one. The fistula test was performed on two of them and was positive (Hennebert's sign)[3] in the deaf ear in one. Most of the patients also had a full battery of vestibular tests with ENG recording but this generally added little to the information acquired by the method described above.

Serological tests for syphilis were performed on two patients and both were nonreactive. Radiologic studies of the temporal bones were done on seven patients, all of which were normal.

Labyrinthectomy was performed in the deaf ear of seven patients with unilateral hearing loss and in one ear of a

TABLE 2. ALLEGED CAUSES OF PRIOR HEARING LOSSES IN PATIENTS WITH DELAYED HYDROPS

	Nadol et al	Wolfson and Leiberman	Schuknecht		
	Ipsilateral	Ipsilateral	Ipsilateral	Contralateral	Total
Early childhood, causes unknown	2	2	4 (2)	5	13
Head trauma	3		(2)		3
Viral labyrinthitis URI	3	1	(2)		4
Mumps	2	2	(1)		4
Mastoiditis and labyrinthitis	1				1
Influenza			1		1
Meningitis				1	1
Diphtheria	1				1
Total	12	5	5	6	28

( ) Previously reported by Nadol et al.

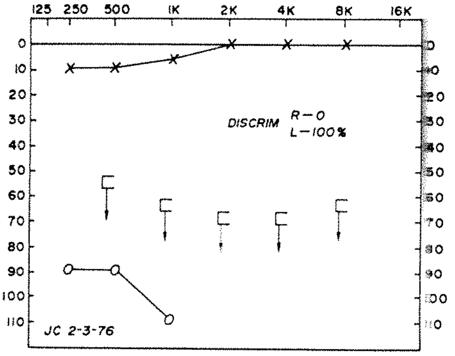

Fig. 1. (Case JC) Audiogram at age 21. He was found to have a profound right hearing loss at the age of six. Vertigo was first experienced at the age of 18.

patient with bilateral hearing loss. This ear was chosen on the basis of a positive Hennebert's sign and absent caloric response to ice water. Postoperatively he had vertigo and nystagmus for several weeks and unsteadiness for two years after which he had no further complaints of vertigo. The method employed was the transtympanic route through the oval window with removal of the utricle and saccule and maceration of the cristae.[4] No perilymph gushers were encountered.

A classical example of ipsilateral delayed endolymphatic hydrops is the following case:

Case JC. At age six, the patient noticed that he could not hear in the right ear. He did not know how long the loss had existed. There had been no illnesses or traumas which could be related to the hearing loss. He was healthy without other symptoms of otological disease until the age of 18 when he felt slightly unsteady for a few days. Six months later he began having episodic vertigo with associated nausea and vomiting. During the next six months, he had five severe attacks and an almost constant sensation of unsteadiness. At the age of 20, he stated that he was somewhat disabled by the unsteadiness but the attacks of vertigo were less severe. At that time, audiometry revealed profound hearing loss on the right and normal hearing on the left. ENG showed a left directional preponderance. Polytomographic radiological studies of the temporal bones were normal. He was advised that a right labyrinthectomy would probably relieve his vertigo, but he declined to have surgery. At the age of 21, he continued to complain of unsteadiness and occasional episodes of vertigo but he had no nausea or vomiting. He noticed that changes in altitude and digital pressure on his right ear caused momentary vertigo. Examination revealed a positive Hennebert's sign on the right ear. Audiometry again showed a profound hearing loss in the right and normal hearing on the left (Fig. 1). He submitted to a right labyrinthectomy. The operation was performed by the transtympanic route. After removal of the incus and stapes, the utricle and saccule were removed through the oval window and the ampulated ends of the semicircular canals were probed with a 3 mm hook. Postoperatively he experienced severe vertigo and had spontaneous nystagmus to the left. Over a period of several weeks the vertigo improved steadily. Two years later (age 23), he still had slight unsteadiness with quick head movements but no further episodes of episodic vertigo. He had no further symptoms of vertigo with altitude changes or on digital pressure on the ear, and the fistula test was negative. There continued to be a fine spontaneous nystagmus to the left. Ice water caloric test gave no responses on the right. Hearing and caloric responses were normal on the left. Polytomographic radiologic studies were normal.

CONTRALATERAL DELAYED ENDOLYMPHATIC HYDROPS

Six patients have been encountered who meet the criteria for contralateral delayed endolymphatic hydrops (Table 3). The criteria for inclusion in this

TABLE 3. CONTRALATERAL DELAYED ENDOLYMPHATIC HYDROPS

	Early History		*Late History*					
	Profound Hearing Loss	*Age*	*Age*	*Fluctuating Hearing Loss*	*Episodic Vertigo*	*Caloric Responses Right*	*Caloric Responses Left*	*Therapies*
1 DR	L	Childhood	14	+	+	DVR	DVR	Steroid
2 KL	L	Childhood	10	+	+	0	DVR	Steroid
3 SP	R	Childhood	30	+	0	DVR	0	Miscel. med.
4 DB	L	Childhood	18	+	0	0	0	Miscel. med.
5 DP	R	Childhood	21	+	0	0	0	Miscel. med.
6 AY	R	15	49	+	0	0	0	Steroid

DVR - Decreased vestibular response; R - Right; L - Left.

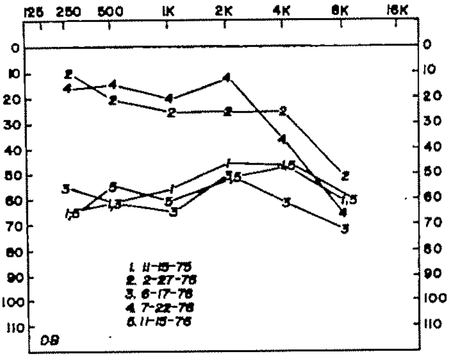

Fig. 2. (Case DB) Patient was found to have a profound left hearing loss at the age of four. At the age of 17 he began having fluctuations of hearing in his right ear. The graph shows pure tone thresholds on five tests over a span of one year (age 17 to 18).

group are: 1) profound hearing loss in one ear, discovered incidentally in childhood or related to some specific disease or trauma and 2) subsequent onset in the opposite ear of fluctuating hearing loss, with or without episodic vertigo of the Ménière's type. The profound unilateral sensorineural hearing losses were discovered incidentally in childhood in five and following meningitis at the age of 15 in one. The losses were distributed equally between right and left ears. The time spans from the discovery of unilateral profound hearing loss to the subsequent onset of contralateral fluctuating hearing loss varied from 5 to 34 years for an average of 17 years. Two of the six patients experienced episodic vertigo along with the contralateral fluctuating hearing losses. It is possible that these two cases represent classical Ménière's disease (idiopathic endolymphatic hydrops) occurring incidentally in their contralateral ears, however their young ages at the time of onset (10 and 14 years) would be unusual for Ménière's disease.

Four patients in this group experienced no vertigo at any time. Three of them had no response to ice water caloric test in either ear. One had a slight response to ice water in the previously deaf ear but no response in the contralateral ear.

The fistula test was performed on two patients and was positive (Hennebert's sign) in the deaf ear of one. Serological tests for syphilis were nonreactive in all six patients. Radiologic studies of the temporal bones were performed on five patients, all of which were normal.

All six patients received a variety of medical therapies including low salt diet, nicotinic acid, meclizene, and histamine injections, and three had one or more courses of steroid therapy. None have shown a clear response to therapy.

The following case history is representative of this group:

Case DB. This patient had congenital idiopathic thrombocytopenic purpura in infancy for which he received multiple transfusions. At about the age of four it was discovered that he had no hearing in his left ear. He was noted to be a clumsy child with poor motor coordination. At the age of 17, he noticed the onset of intermittent tinnitus and hearing loss in his right ear. He had no vertigo. He was treated with a variety of medications including dexamethasone, diazepam, chlorpheniramine, intravenous histamine, low salt diet, and steroids.

The VDRL and FTA serologic tests were negative, lipid profile was normal, glucose tolerance test was normal, and urine and blood analyses were normal. The glycerol test was positive with the speech reception levels improving from 48 to 28 dB in one hour and dropping to 36 dB in four hours. His history was negative for otalgia, otorrhea, noise exposure, head injury, meningitis, thyroid and kidney disease, and severe systemic infections. There was no family history of hearing loss. He had had chicken pox and measles but not mumps. During the following year his hearing losses fluctuated from near normal to 60 dB (Fig. 2). The pure tone threshold patterns were flat and Békésy tracing was type II. Speech discrimination varied from 98% to 84%

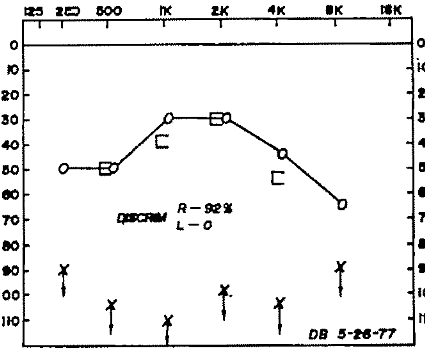

Fig. 3. (Case DB) Audiogram at age 18½ when examined by the author.

and impedence audiometry showed normal compliance. At the last examination (age 18½) audiogram revealed a profound deafness on the left and a moderate sensorineural loss characterized by a flat threshold pattern of 30 to 50 dB on the right (Fig. 3). Speech reception was 32 dB, speech discrimination was 92%, SISI scores were 0 at 500 Hz and 60% at 2 kHz, and there was no tone decay at 500 Hz and 4 kHz. There was no caloric response to ice water in either ear. His hearing losses now occur every three or four months and persist for two or three weeks, but never recover completely. For each episode he is receiving a short course of prednisone therapy.*

DISCUSSION

It is now known that the functional integrity of the inner ear depends upon the maintenance of the special biochemical differences of endolymph and perilymph. The diffusion barrier is maintained by the intercellular junctions of a network of specialized epithelial cells which isolate the endolymphatic system from the surrounding tissues and fluids.[5] The maintenance of endolymph volume and biochemical composition appears to be controlled on the one hand by secretory functions which reside in the stria vascularis of the auditory labyrinth and dark cell areas of the vestibular labyrinth and on the other hand by resorptive functions located in the endolymphatic sac.

There is now an increasing volume of evidence to suggest that the principal cause of endolymphatic hydrops is failure of the resorption mechanism which is presumed to reside in the endolymphatic sac.[6,7] The result is a slow accumulation of endolymph with distention and eventual rupture of the membranous labyrinth. These ruptures permit large volumes of potassium-rich neurotoxic endolymph to contaminate the perilymphatic space. This in turn causes temporary paralysis of the sensory and neural structures, all of which are normally bathed in perilymph. With each rupture the distended membranous labyrinth collapses and heals, permiting the entire process to repeat itself. As the disease progresses there are permanent morphological changes in the sensory and neural structures and persistent deficits in auditory and vestibular function. All of these pathological changes have been observed in temporal bones of subjects with Ménière's disease and in ears of animals in which endolymphatic hydrops had been induced by ablation of the endolymphatic sac.[6-8]

From the clinical standpoint, we can identify two distinct types of endolymphatic hydrops. One may be termed Ménière's disease or idiopathic endolymphatic hydrops, and the other, delayed endolymphatic hydrops. Ménière's disease occurs in ears with previous normal auditory and vestibular function. It may involve one or both ears and usually exhibits both fluctuating hearing loss and episodic vertigo, although one symptom may precede the other by months or years. Ménière's disease is a very common disorder. Stahle et al[9] reported an incidence in Sweden to be 46 per 100,000 population, which in that country, is about four times more common than clinical otosclerosis. Although the etiology of Ménière's disease is not yet known, there is evidence to suggest that some cases may be the result of hypoplasia of the endolymphatic sac, and that it may on occasion be inherited.[10-13]

Delayed endolymphatic hydrops, on the other hand, occurs in patients having preexisting ear pathology. It can be classified into ipsilateral and contralateral types. There is usually a long time lapse, often many years, from the original insult to the onset of symptoms of hydrops. A possible explanation for the hydrops is that the original insult, whatever its cause, had either damaged the endolymphatic sac or blocked the vestibular aqueduct, thus compromising the resorption of endolymph. This concept also implies that some active secretory tissue remains, and furthermore that some auditory and/or vestibular function is present so that symptoms can be elicited.

SUMMARY

The clinical findings in 18 patients

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*Dr. Eugene Rex of Philadelphia has provided past diagnostic and therapeutic data and is continuing the medical management of this patient.

with fluctuating hearing and/or episodic vertigo suggest that endolymphatic hydrops may occur as a delayed manifestation of prior insult to the inner ear. The ipsilateral form of the disease (12 cases) is characterized by the delayed onset of episodic vertigo generated in ears having preexisting profound hearing losses of long duration. It is now evident that there is also a contralateral form of the disease (6 cases) in which affected patients have profound hearing losses of long duration in one ear and subsequently develop fluctuating sensorineural hearing losses in their opposite ears which previously had normal hearing. Some of these patients also have episodic vertigo but others do not, presumably for the reason that vestibular function had been destroyed in both ears at the same time that some prior insult had destroyed the hearing in one ear.

Many of the patients (8 ipsilateral and 5 contralateral) incidentally noticed the unilateral hearing losses in early childhood and no specific causes were evident. Alleged causes in other cases were mumps in one, head trauma in two, influenza in one and meningitis in one.

A possible explanation for the delayed symptoms is that the original insult, whatever its cause, had either damaged the endolymphatic sac or blocked the vestibular aqueduct, thus compromising the resorption of endolymph and the eventual development of hydrops.

Labyrinthectomy is the treatment of choice for the patients with ipsilateral delayed endolymphatic hydrops who are disabled by recurring episodic vertigo. No satisfactory treatment has been found for the patients with the contralateral form of the disease.

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PATHOLOGY OF CHRONIC OTITIS MEDIA

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A review of 800 pathological temporal bones collected from autopsy cases revealed 333 (41.6%) to have some type of otitis media; purulent otitis media (52.5%), serous otitis media (6%), mucoid otitis media (4.5%), and chronic otitis media (36.9%). The 123 temporal bones with chronic otitis media were further studied and found to have granulation tissue, cholesteatoma, cholesterin granuloma, bone changes, and fibrosis. Other findings included tympanic membrane perforation, tympanosclerosis, metaplasia of the epithelium with subepithelial glandular formation, suppuration, labyrinthitis, and evidence of complications of chronic otitis media (meningitis, subdural abscess, brain abscess, petrositis, and endolymphatic hydrops). From this study it was concluded: 1) chronic otitis media occurred quite frequently, from a histological standpoint, in the absence of tympanic membrane perforation; 2) granulation tissue in temporal bones was found much more frequently in chronic otitis media than was cholesteatoma; and 3) complications and sequelae of otitis media tended to occur more commonly secondary to granulation tissue than to cholesteatoma.

Otitis media represents one of the most prevalent forms of infectious disease. It is a worldwide health problem which is still prevalent in the modern antibiotic era. The socioeconomic impact is immense and due not only to the inflammatory process, but to the associated hearing loss. A significant portion of the estimated 13 million Americans suffering from hearing loss have associated otitis media. Contributions to the subject of otitis media are numerous, yet complete understanding of the entire problem is lacking. Significant disagreement exists regarding etiology, epidemiology, natural history, pathology, and treatment. The pathology of chronic otitis media (COM) based on a study of 123 temporal bones will be reviewed and discussed.

BACKGROUND

Granulation tissue, cholesteatoma, osseous changes, tympanosclerosis, cholesterin granuloma, fibrosis, glandular formation, and epithelial metaplasia have all been described in COM.[1] Palva et al[2] summarized the histopathological findings of mastoiditis as new bone formation, epithelial metaplasia (stratified ciliated columnar epithelium and mucoid glands), granulation tissue, and formation of cholesterin granuloma.

In his textbook, Schuknecht[3] described the pathology of COM. The important findings he identified were mucosal edema and ulceration, formation of polyp and granulation tissue, rarefying osteitis of the ossicles, otic capsule and mastoid bone, formation of keratoma, epidermization, fibrosis, fibrocystic and fibroosseous sclerosis, and tympanosclerosis.[4,5] Schuknecht[6] also divided COM into active, chronic inflammation (increased vascularity of mucosa and submucosa, acute and chronic inflammatory cells, and ulcerations in the mucosal lining leading to granulation tissue) and healed chronic inflammation (fibrosis, new bone formation).

Friedmann[7] reviewed bone chips from 770 mastoidectomy procedures and identified granulation tissue as the primary pathological process in 49% of the cases, cholesteatoma as a primary pathological process in 20% of the cases, and cholesterin granuloma as the primary pathological process in 5.5% of the cases. He

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also observed cholesterin granuloma to occur only in uninfected ears.

Perhaps the earliest alteration seen in COM is epithelial metaplasia of the normal cuboidal epithelium to columnar ciliated epithelium with goblet cells and gland-like structures occurring as early as 14 days into the disease process. This metaplastic change also occurs in other forms of otitis media and is not limited to COM.[8]

Cholesteatoma is defined by Friedmann[7] as "a cystic structure lined by keratinizing stratified squamous epithelium resting on fibrous stroma of variable thickness which may contain some elements of the original mucous lining." More simply, Schuknecht[3] stated, "it is the accumulation of exfoliated keratin in the middle ear or pneumatized areas of the temporal bone, arising from keratinizing squamous epithelium . . ." Lim and Saunders[9] observed that cholesteatoma was morphologically identical to tympanic membrane epidermis except for a greater number of Langerhans' cells in the former.

Cholesteatoma was first described (pearly tumor) by Cruveilhier in 1829[10] and named by Muller in 1938.[11] It currently plays a significant role in the natural history and morbidity of COM.[12]

Granulation tissue also plays a major role in the natural history and morbidity of COM and is believed by some to be at least more prevalent if not more significant than cholesteatoma.[12] It is defined as "newly formed, highly vascularized connective tissue with a component of acute inflammatory exudation."[13] It consists of proliferated fibroblasts and vascular endothelium which invade, are associated with exudate and hemorrhage, and result in tissue damage. With maturation, granulation tissue becomes more dense with increased collagen and reticular formation. It is self-perpetuating in that it reduces the effectiveness of medical therapy and ventilation of the cells.[13]

Less frequently encountered but of significant interest and importance is cholesterin granuloma. This entity was first reported and described by Ranger[14] and appears to be a foreign body reaction to the breakdown products of blood (particularly cholesterol crystals). It has been identified in chronic granulomatous mastoiditis and chronic suppurative otitis media[15] and experimentally produced by obstructing the air channel to the humerus of a chicken[16] and by injecting sterile suspensions of cholesterol into the middle ear cleft of guinea pigs.[17]

Osseous changes occur as sequelae of otitis media and continue to occur throughout the course of the disease. These changes include osteitis, necrosis, reabsorption, and new bone formation.[17,18] Although pressure changes and anoxia have been considered of major import, current thinking gives more support to increased vascularity, enzymes, cellular activity (histiocytes, osteoclasts, and osteoblasts), and prostaglandins.[19-26] Granulation tissue appears to play an equal if not more important role in the observed osseous changes than cholesteatoma.[12,19,21,27,29]

Tympanosclerosis is usually observed as a sequela of recurrent acute otitis media but is also identified clinically and histologically in COM.[4,5] First described by von Tröltsch in 1877[30] it appears to be a hyalinization of the submucosal layers, perhaps based on a hypersensitivity phenomenon, which may proceed to obliterate the middle ear cleft and fix the ossicles.[3]

TERMINOLOGY

According to Senturia,[31] the proper use of terminology and classification of effusions by investigators throughout the world is necessary if we are to understand and eradicate this widespread group of diseases. Sheehy[32] has classified serous otitis media into two groups: 1) serous (or secretory) otitis media (acute and chronic), and 2) suppurative otitis media (acute, subacute, and chronic). Thorburn[33] described two subgroups of chronic middle ear inflammation: 1) persistent perforation syndrome, and 2) persistent tubotympanic mucosal infection. More recently Paparella and Juhn[34] described a classifi-

TABLE 1. SEX AND AGE DISTRIBUTION OF CHRONIC OTITIS MEDIA CASES

	Sex		*Age*		
Type	*M*	*F*	*M*	*F*	*Total*
Chronic active					
Generalized	23	11	54.7	38.8	49.6
Local	25	10	58.0	60.5	58.7
Chronic Inactive	12	9	55.6	61.4	58.1
Total	60	30	56.3	53.4	55.3

cation of otitis media and observed that certain forms can be interrelated and can occur in a continuum. Serous otitis media (SOM), both acute and chronic, and mucoid otitis media (MOM), usually chronic, are clinically considered to be nonsuppurative middle ear inflammatory problems with somewhat similar etiologies. SOM appears to be more of a transudate while MOM is the result of active secretion by secretory cells, goblet cells, and subepithelial glands. Purulent otitis media (POM) involves suppuration of the middle ear cleft with erythema and bulging of the tympanic membrane. Chronic otitis media (COM) refers to an inflammatory process within the middle ear cleft associated with *irreversible* tissue pathology. It may be active, with ongoing suppuration or inactive demonstrating sequelae of a previous infection.

RESULTS

In the past ten years, 800 temporal bones have been processed by fixation, decalcification and celloidin embedding technique. These 800 temporal bones were collected from autopsy cases with some history or findings of ear disease or suspected ear damage from drugs, trauma, or systemic disorder. The blocks were cut at 20μ sections and stained with H & E or special stains if indicated.

Following thorough examination of these 800 temporal bones, 333 (41.6%) were found to have some type of otitis media: 175 POM (52.5%), 20 SOM (6.0%), 15 MOM (4.5%), and 123 COM (36.9%). The designation of chronic otitis media was dependent upon finding *irreversible* changes including granulation tissue, cholesteatoma, cholesterin granuloma, bone changes, or fibrosis in the reviewed sections. Also present in many cases were tympanic membrane perforation, tympanosclerosis, metaplasia of the epithelium with subepithelial glandular formation, suppuration, labyrinthitis and evidence of complications of chronic otitis media (meningitis, subdural abscess, brain abscess, petrositis, and endolymphatic hydrops). It was these 123 temporal bones of chronic otitis media that constituted this study.

The chronic otitis media temporal bones (123 temporal bones from 90 patients) were further classified under three categories according to the degree and activity of pathological changes in the middle ear cleft as follows:

1. Chronic active type: 96 ears (78.1%) from 69 patients.

A) Generalized form: There is present generalized suppuration in the middle ear cleft in addition to those findings listed as compatible with COM.

B) Focal form: These temporal

TABLE 2. INCIDENCE OF PATHOLOGICAL TISSUES

	Chronic Active		*Chronic*		
Number of Ears	*Generalized (46)*	*Focal (50)*	*Inactive (27)*	*Total (123)*	*%*
Fibrosis of mucoperiosteum	31 (67%)	44 (88%)	19 (70%)	94	76.4
Granulation tissue	43 (93%)	29 (58%)	13 (48%)	85	69.1
Osteitis	46 (100%)	44 (88%)	21 (78%)	111	90.2
Subepithelial glands	26 (57%)	18 (36%)	6 (22%)	50	40.7
Tympanosclerosis	16 (35%)	11 (22%)	7 (26%)	34	27.6
Polyp	19 (41%)	4 (8%)	0	23	18.7
Cholesteatoma	15 (33%)	2 (4%)	1 (4%)	18	14.6
Cholesterin granuloma	13 (28%)	2 (4%)	1 (4%)	16	13.0
Tympanic membrane perforation	21 (46%)	1 (2%)	2 (7%)	24	19.5

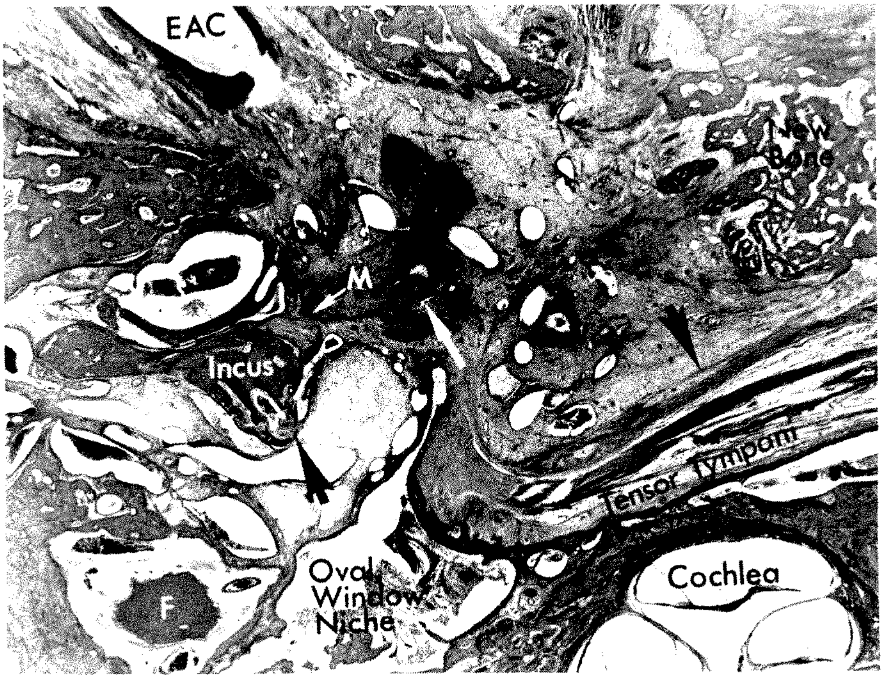

Fig. 1. Granulation tissue obliterating the middle ear space in an 88-year-old male. Malleus head (M) is almost completely destroyed through resorption. Body of incus and bony covering of tensor tympani muscle are eroded by inflammatory process (arrows). New bone is seen on anterior epitympanic wall. Oval window niche is filled with purulent fluid. F - Facial nerve; EAC - External auditory canal. (H & E, X10)

bones demonstrated focal suppuration with local accumulations of purulent fluid in the middle ear cleft as well as those findings listed as compatible with COM.

2. Chronic inactive type: 27 ears (21.9%) from 21 patients. These temporal bones demonstrated no evidence of suppuration but generalized or focal changes of chronic inflammatory reaction in the middle ear cleft.

The sex distribution of COM is shown in Table 1 with a male to female ratio of 2 to 1. The average age of the patients was 55.3 years. Two thirds of the 90 patients with COM in this study

TABLE 3. DISTRIBUTION OF GRANULATION TISSUE

	Chronic Active		*Chronic*		
	Generalized	*Focal*	*Inactive*	*Total (%)*	
Epitympanum	35 (76%)	18 (36%)	4 (15%)	57	46.3
Round window niche	35 (76%)	13 (26%)	8 (30%)	56	45.5
Prussak's space	33 (72%)	11 (22%)	2 (7%)	46	37.4
Mastoid bone	28 (61%)	17 (34%)	1 (4%)	46	37.4
Oval window niche	28 (61%)	13 (26%)	3 (11%)	44	35.8
Facial recess	27 (59%)	13 (26%)	4 (15%)	44	35.8
Tympanic sinus	28 (61%)	9 (18%)	3 (11%)	40	32.5
Promontory	28 (61%)	10 (20%)	0	38	30.9
Antrum	24 (52%)	12 (24%)	0	36	29.3
E-tube orifice	14 (30%)	2 (4%)	0	16	13.0
Petrous bone	4 (9%)	5 (10%)	0	9	7.3

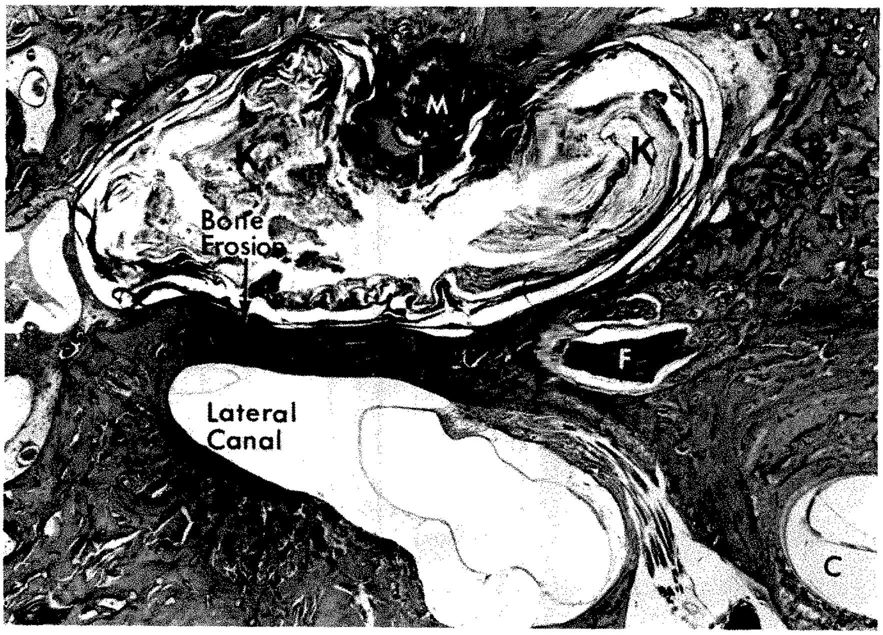

Fig. 2. Cholesteatoma sac of left epitympanic cavity in a 50-year-old female. Keratin flakes with purulent fluid (K) and widened epitympanic cavity are shown. Incus (I) is nearly destroyed and malleus (M) eroded by cholesteatoma epithelium and underlying inflammatory granulation tissue. Bony erosin of medial epitympanic wall is seen. F - Facial nerve. (H & E, X9)

had unilateral otitis media and one third had bilateral otitis media.

The most frequently encountered pathological tissues in all cases studied were fibrous thickening of the mucoperiosteum, granulation tissue, and osteitic changes of the ossicles, mastoid bone, and otic capsule (Table 2).

The most frequent pathological tissue in the generalized form of the chronic active type was osteitis (100%) followed in frequency by granulation tissue (93.5%). Granulation tissue occurred in approximately 60% of the focal form of chronic active type and 50% of chronic inactive type of otitis media. The epitympanic cavity, mastoid air cells, and round window niche were the most common sites for the granulation tissue. In over 80% of cases of the generalized form of chronic active type, the epitympanum and round window niche were involved with granulation tissue. In the focal form of the chronic active type, granulation tissue was found in the epitympanum and mastoid air cells in 60% of the cases. The round window niche was the most commonly involved site in the chronic inactive type (Fig. 1 and Table 3).

Eighteen cases of cholesteatoma were found in the 123 temporal bones studied

TABLE 4. DISTRIBUTION OF CHOLESTEATOMA

	Chronic Active		*Chronic*		
	Generalized	*Focal*	*Inactive*	*Total*	*(%)*
Epitympanum	13	1	1	15	83.3
Meso-, Hypotympanum	12	1		13	72.2
Antrum	6			6	33.3
Mastoid cells	5			5	27.8
Number of cases	15	2	1	18	

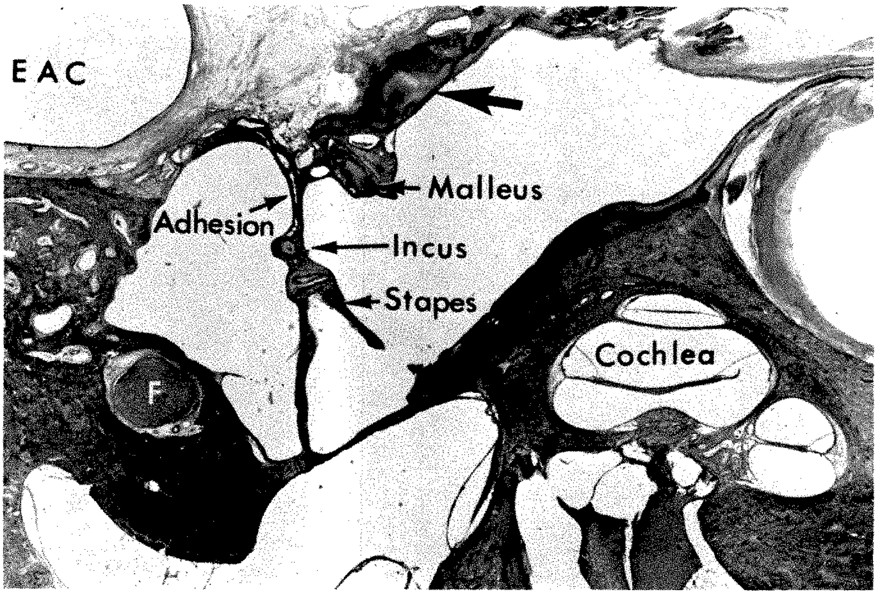

Fig. 3. Tympanosclerotic plaque (large arrow) and thick fibrocystic connective tissue, obliterating anterior sulcus of external auditory canal (EAC) are seen. Malleus handle shows rarefying osteitis and fibrous tissue replacement. Dense fibrous adhesion is seen between thickened fibrotic tympanic membrane and partially eroded long process of incus. F - Facial nerve. (H & E, X7)

(14.6%). Of these 18 cases, 15 (83.3%) were found in the generalized form of the chronic active type, while only 4% of the focal form of the chronic active type had cholesteatoma. Epitympanic cavity, hypotympanic cavity and mesotympanic cavity were the usual sites of cholesteatoma (Fig. 2 and Table 4).

Tympanosclerotic foci were found in 34 of the 123 cases of COM (27.6%); 16 cases in the generalized form of the chronic active type, 11 cases in the focal form of the chronic active type, and 7 cases in the chronic inactive type. The tympanic membrane was the most commonly involved site (82.4%) (Fig. 3 and Table 5). Tympanosclerosis also was observed in the middle ear (8.9%) and was found to involve the ossicles (3.2%). Tympanosclerosis was also observed in the mastoid cavity in 3.2% of cases. In this temporal bone review, however, tympanosclerosis did not have the anatomical appearance or location to suggest interference with sound conduction of the middle ear.

Cholesterin granuloma was found in 15 cases of COM, mostly in the generalized form of the chronic active type (13 cases). It was located in the tympanic cavity (nine cases) and in mastoid air cells (eight cases) (Fig. 4).

TABLE 5. DISTRIBUTION OF TYMPANOSCLEROTIC LESIONS IN DIFFERENT TYPES OF CHRONIC OTITIS MEDIA

	Chronic Active		*Chronic*		
	Generalized	*Focal*	*Inactive*	*Total*	*(%)*
Tympanic membrane	12	10	6	28	82.4
Tympanic cavity	8	3		11	32.4
Ossicles	3	1		4	11.8
Mastoid cells	3		1	4	11.8
Number of cases	16	11	7	34	

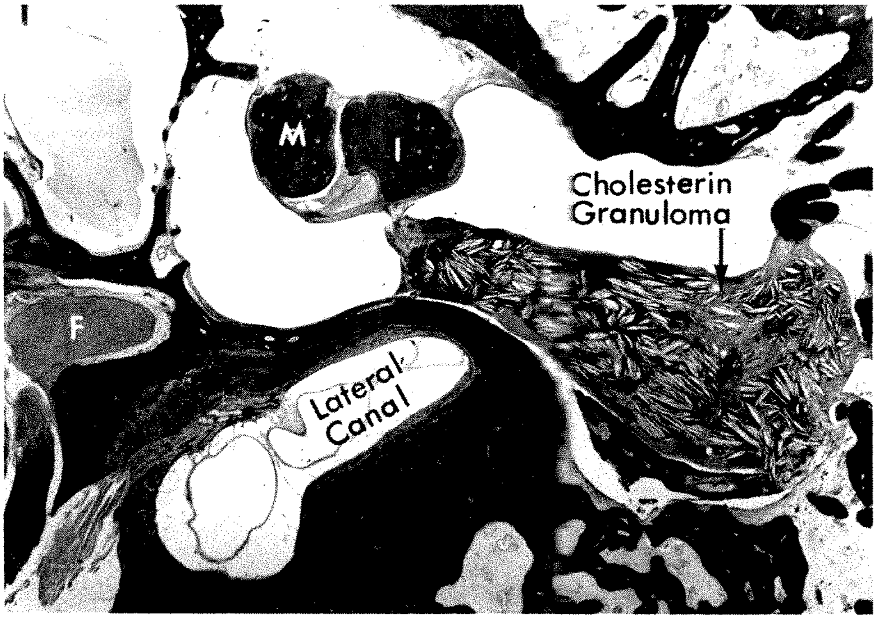

Fig. 4. Cholesterin granuloma of the attic-aditus-antral space in a 59-year-old male showing cholesterol clefts developing inside of serohemorrhagic granulation tissue. Inflammatory hemorrhagic exudate is seen close to the cholesterin granuloma (arrow). Mastoid air cell space is obliterated by dense fibrocytic connective tissue. F - Facial nerve; M - Malleus; I - Incus. (H & E, X6)

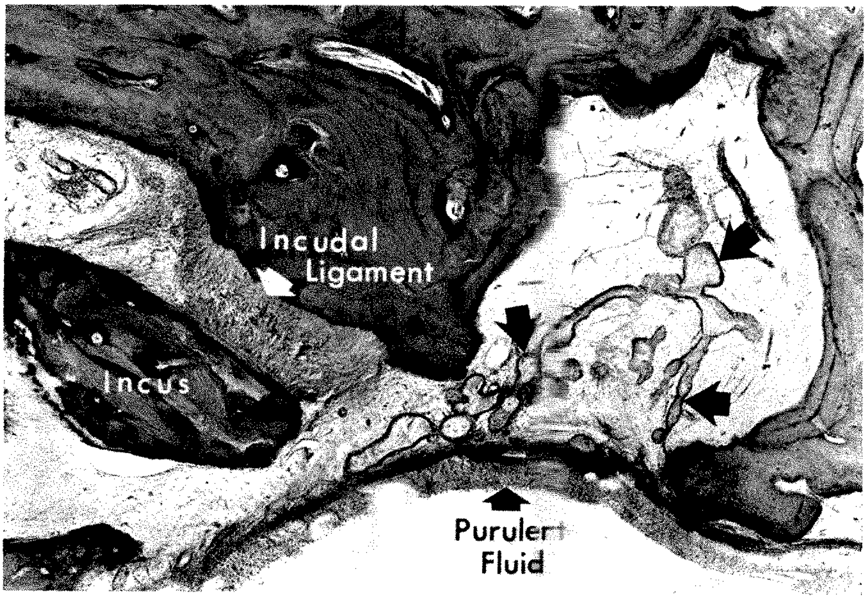

Fig. 5. Subepithelial glandular structures (arrows) of the periantral space in a 54-year-old male. Gland and duct-like structures are lined by flat or cuboidal cells, surrounded by vascular loose connective and chronic inflammatory cells, mostly lymphocytes. (H & E X35)

TABLE 6. INVOLVEMENT OF OSSICLES IN CHRONIC OTITIS MEDIA

	Ossicle Destruction	*All Ossicles*	*Malleus*	*Incus*	*Stapes*
COM without cholesteatoma N=105					
Chr. Active Generalized N=31	31	25	26	29	30
Focal N=48	38	7	11	38	23
Chr. Inactive N=26	14	0	2	15	2
COM with cholesteatoma N=18					
Chr. Active Generalized N=15	15	14	14	15	15
Focal N=2	2	0	0	2	1
Chr. Inactive N=1	1	0	0	1	0
Total No. N=123	101	46	53	100	71
(%)	82.1	37.4	43.1	81.3	57.7

Subepithelial glandular formation was found in 50 cases of COM (40.7%). Half of these cases were in the generalized form of the chronic active type (26 cases), 18 cases were found in the focal form of the chronic active type, and 6 cases in the chronic inactive type. The lesion was found both in the tympanic cavity (44 cases) and in the mastoid air cells (33 cases) (Fig. 5).

Ossicular involvement was found in 101 cases (82.1%) of COM. The incidence of ossicular involvement in the generalized form of the chronic active type was 100% while there was an incidence of ossicular involvement in 80% of the focal form of the chronic active type, and 55.6% in the chronic inactive type. The incus was most commonly involved (100 cases, 81.3%) followed in frequency by the stapes (71 cases, 57.7%) and malleus (53 cases, 43.1%). All three ossicles were involved in 46 cases (37.4%), mostly in the generalized form of the chronic active type (39 cases) (Table 6).

One case of malleus fixation to the scutum and one case of incus fixation

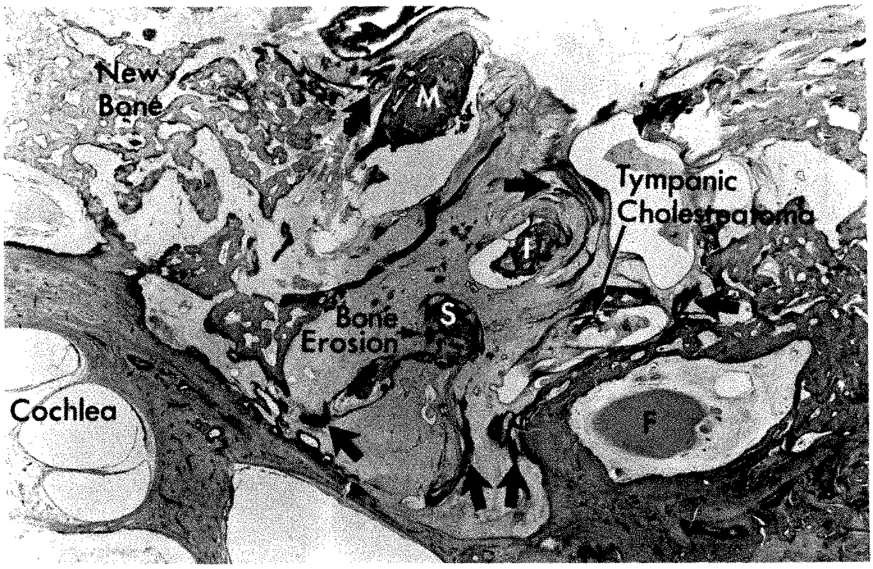

Fig. 6. Osseous changes of middle ear space in a 75-year-old male showing rarefying osteitis of malleus, incus, and stapes. Ossicles are fixed by dense fibrous tissue, tympanosclerotic plaques (arrows) and new bone formation. Small intratympanic cholesteatoma is seen on facial canal (F). (H & E X9)

TABLE 7. COMPLICATIONS OF CHRONIC OTITIS MEDIA

	Chronic Suppurative		*Chronic*	
	Generalized *46 ears/34 pts*	*Focal* *50 ears/35 pts*	*Inactive* *27 ears/21 pts*	*Total (%)* *123 ears/90 pts*
Meningitis	6 (13.0%)	—	—	6 (4.9%)
Brain Abscess	3 (6.5%)	—	—	3 (2.4%)
Subdural Abscess	3 (6.5%)	—	—	3 (2.4%)
Cochlear Hydrops	8 (17.4%)	9 (18%)	5 (18.5%)	22 (17.9%)

to the medial wall of the attic were found. In the focal form of the chronic active type, two cases of incudomalleolar fixation and two cases of incus-incudal fossa fixation were found.

Bony erosion of the periosteal layer of the lateral semicircular canal was found in four cases of the generalized form of the chronic active type of COM. Osteitis of the mastoid air cells was noted in 52 cases (61.9%); there were 22 cases in the focal form and 20 cases in the generalized form of the chronic active type. In the petrous area osteitic changes were found in 14 cases (16.7%); it was most common in the generalized form of chronic active type (11 cases).

The fallopian canal was partially eroded in 38 cases (30.9%); 22 cases of these were in the generalized form while 14 cases were in the focal form of the chronic active type. Seven temporal bones studied had undergone previous mastoidectomy, four simple and three modified procedures. Complications of COM included meningitis, brain abscess, subdural abscess, and cochlear hydrops. All cases of endolymphatic hydrops had associated histological findings of granulation tissue in the round window niche but in most cases absence of labyrinthitis. Intracranial complications of meningitis (6/123 temporal bones), brain abscess (3/123), and subdural abscess (3/123) were uniquely limited to temporal bones with granulation tissue. Some of these temporal bones also contained cholesteatoma (Table 7).

Labyrinthitis was found in 25 cases of COM (20.3%). Of these, 22 cases (88%) were found in the generalized form of the chronic active type and 2 cases (8%) were in the chronic inactive type. In the generalized form, 47.8% of cases had some type of labyrinthitis: 16 serous, 4 purulent, and 2 in the form of ossificans (Table 8).

The round window membrane was infiltrated with inflammatory cells in 11 cases (8.9%) of COM studied, all of which were in the generalized form of the chronic active type (Fig. 7). In 22 cases (17.9%), the round window membrane was convex and fixed by contracture of mature fibrous connective tissue in the round window niche. The round window niche was frequently obliterated by thick fibrous granulation tissue.

Petrositis was found in 17 cases of COM. Thirteen of these cases (76.5%) were in the generalized form of the chronic active type, and two cases each were found in the focal form of the chronic active and chronic inactive types. Of those 17 cases, 15 had lesions in the apical region of the petrous bone and 4 cases had lesions in the perilabyrinthine region of the petrous bone.

TABLE 8. DISTRIBUTION OF LABYRINTHITIS

	Chronic Active		*Chronic*		
	Generalized	*Focal*	*Inactive*	*Total*	*(%)*
Serous	16	1	1	18	72.0
Purulent	4	0	0	4	16.0
Fibrous	0	0	1	1	4.0
Osseous	2	0	0	2	8.0
Total	22	1	2	25	

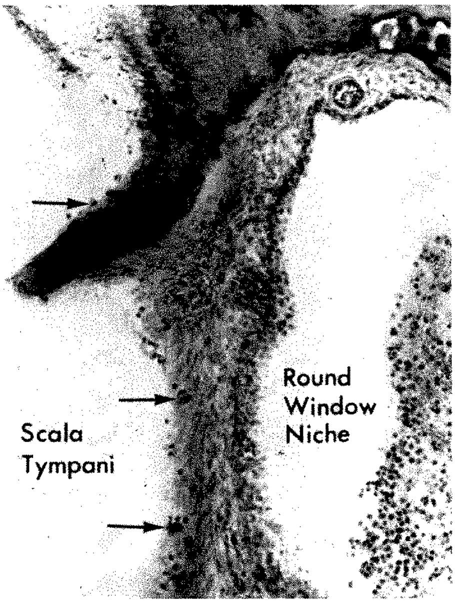

Fig. 7. COM with round window membrane invasion of inflammatory cells in a 22-month-old male. RWM is thickened by capillary dilatation, hyperplasia of outer epithelial layer, proliferation of fibrous layer and infiltration of inflammatory cells, mostly neutrophils. Round window niche shows seropurulent exudate. Serofibrinous exudate and inflammatory cells are seen in the scala tympani (arrows). (H & E X150)

DISCUSSION

Our histopathological findings in COM include the irreversible findings of granulation tissue, cholesteatoma, cholesterin granuloma, osseous changes, subepithelial fibrosis, and fibrous adhesions. Epithelial metaplasia, subepithelial glandular formation, tympanosclerosis, suppuration, and evidence of complications of COM such as meningitis, subdural abscess, brain abscess, petrositis, labyrinthitis, and endolymphatic hydrops were also encountered. Of particular interest was the low incidence of associated tympanic membrane perforation (19.5%) seen in temporal bones displaying other manifestations of COM. This finding is somewhat in conflict with clinical observations that COM is always associated with a permanent tympanic membrane perforation. This feature also confirms recent clinical findings of unsuspected COM in ears with intact tympanic membranes being operated for other causes.[35] The clinician should be alerted to the possibility of "silent" chronic otitis media as the etiologic basis for aural symptomatology such as sensorineural hearing loss (fluctuating or progressive), vertigo, and tinnitus. Of the 90 patients (123 ears) in this study, only 24 patients (36 ears) had symptoms of otologic disease recorded on their charts. These symptoms included in order of decreasing frequency, hearing loss, discharge, tinnitus, and pain. Only nine patients had a history of childhood otitis recorded.

Cholesteatoma, in this temporal bone study, was a relatively infrequent and fairly localized finding compared to the frequent and rather generalized finding of granulation tissue. The granulation tissue encountered was both of the mature type and the immature type. Granulation tissue classified as mature was more fibrous and less cellular than the highly vascular and highly cellular type classified as immature. The spectrum of immature to mature granulation tissue has also been observed clinically. Both the prevalence (granulation tissue more frequent than cholesteatoma) and distribution (granulation tissue more generalized than cholesteatoma) support clinical observations in surgery for chronic otitis media.[7,12,28,29] The frequency and generalized distribution of granulation tissue, coupled with its cellular and biochemical activity, play a key role in the natural history and complications observed clinically and histopathologically in chronic otitis media. Chronic otitis media resulting in labyrinthitis with subsequent sensorineural hearing loss and endolymphatic hydrops has been reported from both a clinical and histpathological standpoint.[36,37] Our current temporal bone study supports these earlier works and identifies the frequency with which granulation tissue involves the round window niche and distorts the round window membrane.

Osseous changes observed in these 123 temporal bones included osteitis, osteoneogenesis, bone erosion, and necrosis. The incidence of bony changes in specimens studied was 90.2% with the involvement paralleling the severity of the inflammatory process. Other osseous changes observed were in the form of ossicular erosion (incus most frequently, stapes next in frequency, malleus least in frequency), necrosis, and osteoneogenesis were seen in both the presence and absence of cholesteatoma. These findings support clinical and experimental studies on osseous changes in chronic otitis media and stress the fact that the presence of cholesteatoma is not necessary for bony changes to occur.[19,21,27]

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AMERICAN ACADEMY OF OTOLARYNGOLOGY
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The Research Forum, under the joint sponsorship of the Committee for Research in Otolaryngology of the American Academy of Otolaryngology and the Association for Research in Otolaryngology, will be held October 6-7, 1979 in Dallas, Texas. Those interested in having their papers considered for the program should send two copies of a one-page abstract no later than May 18, 1979 to: Robert Mathog, MD, Professor and Chairman, Department of Otolaryngology, Wayne State University School of Medicine, 540 E. Canfield Avenue, Detroit, MI 48201.

Residents interested in submitting for the Awards competition for AAO also must submit their papers postmarked no later than April 13, 1979 to: F. R. Kirchner, MD, Professor of Otolaryngology, University of Kansas School of Medicine, Kansas City, KS 66103.

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SELECT TOPICS IN HEAD AND NECK ONCOLOGY

A postgraduate course, "Select Topics in Head and Neck Oncology" sponsored by the Head and Neck Service of the Memorial Sloan-Kettering Cancer Center will be held February 1-3, 1979. For further information write: Jatin P. Shah, MD, Head and Neck Service, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021.

Ann Otol 87:1978

SUDDEN OR FLUCTUATING HEARING LOSS AND VERTIGO IN CHILDREN DUE TO PERILYMPH FISTULA

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Five cases are presented of children with rapid onset of sensorineural hearing loss, disequilibrium, or both, who were found at exploratory tympanotomy to have a perilymph fistula. Four of the children had histories suggesting that antecedent barotrauma or physical exertion contributed to the development of the fistula. One child with congenital unilateral craniosynostosis had a residual temporal bone abnormality on the same side as the perilymph fistula. Two children had identifiable anatomic abnormalities in the middle ear. A classification of perilymph fistula is proposed that describes a congenital, an acquired and a combined type of fistula. Inner ear fluid dynamics and patency of the cochlear aqueduct appear to be important factors in pathogenesis. Children with unexplained fluctuating or sudden onset of sensorineural hearing loss, and children with unexplained disequilibrium or vertigo should be suspected of having a perilymph fistula. The history can be singularly important in raising the suspicion that a perilymph fistula may be present. Although audiometric, vestibular, and radiographic studies can be helpful, there is no way to prove the presence or absence of a fistula without directly viewing the middle ear. Tympanotomy with repair of the fistula does not assure improvement in hearing.

Several years after the description of poststapedectomy perilymph fistulae, it became evident that similar fistulae can occur in individuals who have not had prior otologic surgery. There is growing evidence that such intracochlear, round, or oval window perilymph fistulae may cause fluctuating or rapid-onset hearing loss, as well as episodic disequilibrium. Barotrauma, severe head injury, and a rapid increase in cerebrospinal fluid (CSF) pressure have all been implicated as causal factors in the development of perilymph fistulae. Thus far, almost all of the cases of perilymph fistulae that have been reported occurred in adults.

Five cases of perilymph fistula, all occurring in children, are now being reported. The cases were discovered within an 18-month period. None of the children had previously had major otologic surgery or head injury.

CASE REPORTS

Case 1. A six-year-old male rapidly developed hearing loss in his left ear. On the day that this occurred he had been feeling well and had no fever, malaise, otalgia, tinnitus, or vertigo. There was no history of antecedent infection. On the day before the hearing loss was noticed, he had been on an airplane, and after the plane landed the boy's mother thought that her son was having difficulty hearing. The past medical history was relevant in that three years previously he had had acute right otitis media, then developed disequilibrium and vertigo and was diagnosed as having had acute right labyrinthitis. Soon after the right ear infection resolved, he had a bilateral myringotomy with insertion of tympanostomy tubes. Ten months before the sudden hearing loss developed in the left ear, the boy had been seen for routine otologic follow-up and at that time both tympanostomy tubes had been extruded, the eardrums were intact, and an audiogram (Fig. 1A) revealed a moderate to severe sensorineural hearing loss in the right ear and hearing within normal limits with a mild air-bone gap for the low frequencies in the left ear.

On examination in the emergency room the child was found to have no evidence of upper respiratory infection and there was no sign of infection in either ear, although the left tympanic membrane appeared to be slightly retracted. The results of the standard Romberg test were negative. The tandem Romberg

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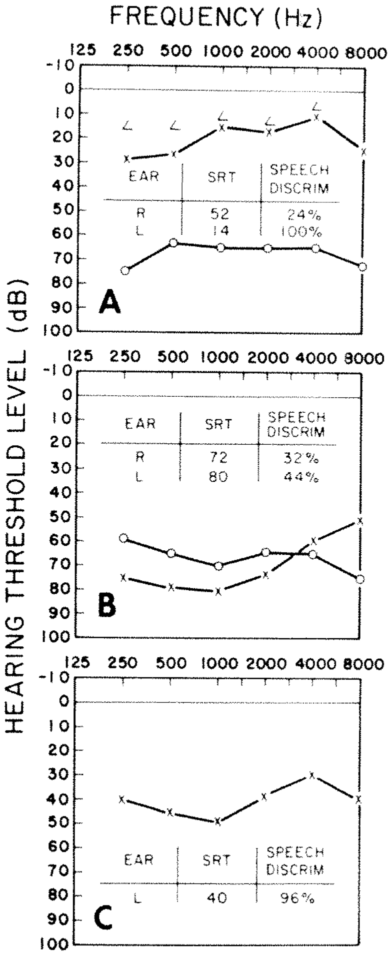
Presented at the meeting of the American Otological Society, Inc., Palm Beach, Florida, April 23-24, 1978.



A

EAR	SRT	SPEECH DISCRIM
R	52	24%
L	14	100%

B

EAR	SRT	SPEECH DISCRIM
R	72	32%
L	80	44%

C

EAR	SRT	SPEECH DISCRIM
L	40	96%

Fig. 1. (Case 1) Audiograms. A) Ten months before hearing loss occurred in left ear; B) At time rapid onset left-sided hearing loss occurred; C) Two months postoperative.

test elicited unsteadiness, although he did not specifically fall to either side. There was no spontaneous nystagmus, and the results of cranial nerve tests were normal as were the results of tests for cerebellar function. No nystagmus or subjective sensation of vertigo could be elicited with positional tests.

The patient was immediately admitted to the hospital for further diagnostic evaluation after an audiogram (Fig. 1B) revealed significant sensorineural hearing impairment in the left ear. Tympanograms revealed normal compliance in both ears, -300 mm H_2O pressure in the left ear, and $+20$ mm H_2O pressure in the right ear. Electronystagmography (ENG) was incomplete in that the patient could not accurately perform calibration tests. However, responses to caloric irrigation were relatively reduced and nearly absent in the right ear. A fistula test in the left ear performed during the ENG recording was negative. The results of the posturography examination were within normal limits.

Based mostly on the apparent association between the rapid onset of hearing loss and the insult to the inner ear that may have been suffered during airplane descent, it was considered that a perilymph fistula in the left ear might have caused the sudden hearing loss. Hence, it was decided to perform a left exploratory tympanotomy on the day following admission. No fistula was identified in the region of the round window. However, a deep oval window niche was noted and the anterior crus of the stapes was abnormal (Fig. 2). The obturator foramen was extremely small and a definite leak of clear fluid could be seen emanating from the region of the anterior edge of the footplate.

Adipose tissue obtained from the earlobe was utilized to close the fistula, and, as a precaution, the mucous membrane in the round window niche was partially removed and adipose tissue was also placed against the round window membrane.

Following surgery, hearing in the left ear temporarily improved for two months until the boy had usable hearing in the left ear (Fig. 1C). However, four months after surgery, hearing worsened to the preoperative level. Since the child was thought to have a persistent or recurrent perilymph fistula, a left exploratory tympanotomy was again performed, but no fistula was evident and only dense fibrosis could be seen at the region of the anterior footplate of the stapes.

One year following surgery the child's hearing thresholds were unchanged, he has been rehabilitated with a hearing aid in the left ear, and attends a school for handicapped children.

COMMENT. It is possible that the anterior footplate of the congenitally abnormal stapes was more susceptible than a normal stapes to the formation of a fistula when subjected to middle ear barotrauma. The possibility that the stapes abnormality was bilateral was considered. It was also thought that the previous right-sided otitis media that proceeded to labyrinthitis and then sensorineural hearing loss may have been related to an undetected right-sided perilymph fistula. Temporal bone tomograms were obtained but no specific abnormality was detected. After hearing had improved in the left ear, an exploratory tympanotomy was performed on the right ear and the same stapes abnormality was found; a fistula was identified and repaired, but there was no hearing improvement in the right ear.

Case 2. A 14-year-old male wind-instrument player was troubled by episodic vertigo and disequilibrium for two months prior to being examined and had been diagnosed as having Ménière's disease. He was aware of decreased hearing in his left ear, although he had no

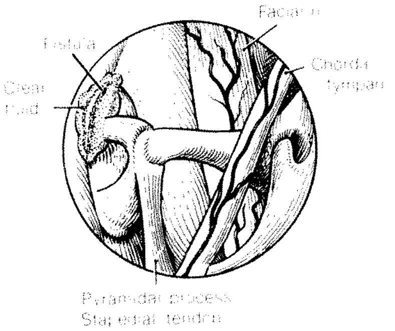


Fig. 2. (Case 1) Abnormal stapes seen in left ear. The anterior crus is straight rather than being curved and it joins the central portion rather than the anterior edge of the footplate.

tinnitus. Significant past medical history included the fact that the boy had undergone a neurosurgical procedure in his first year of life for correction of "craniosynostosis" and at that time the neurosurgeon reported finding a malformation of the left ethmoid and sphenoid bones.

Physical examination revealed no abnormalities except decreased hearing in the left ear, and a positive fistula test in the left ear. An audiogram (Fig. 3A) indicated the presence of a left-sided moderate sensorineural hearing loss. The results of ENG and posturography were indicative of impaired function in the left peripheral vestibular system. Temporal bone polytomography revealed that the left internal auditory canal was larger than the right; there was left craniosynostosis with a residual bony deformity of the petrous portion of the left temporal bone.

A left-sided perilymph fistula was considered to be a possible cause of the symptoms, and a left exploratory tympanotomy was performed. Dense adhesive bands were seen over the footplate of the stapes and a significant amount of clear fluid was seen at the anterosuperior edge of the footplate. The fluid persistently recollected after gentle suctioning. The fistula was repaired with adipose tissue from the earlobe, and within two weeks after repair of the fistula the symptoms of disequilibrium disappeared. Hearing improved within one month (Fig. 3B), but then gradually returned to the preoperative level about four months following surgery. At one year following repair of the fistula there had been no change in hearing and the symptoms of disequilibrium had not recurred.

COMMENT. Significant increases of intrathoracic pressure by Valsalva's maneuver are required for the playing of a wind instrument. In view of the prior history of craniosynostosis, it can be speculated that this child had an underlying anatomic defect in the left temporal bone that predisposed him to the development of a perilymph fistula when the inner ear was subjected to rapid alterations in CSF pressure.

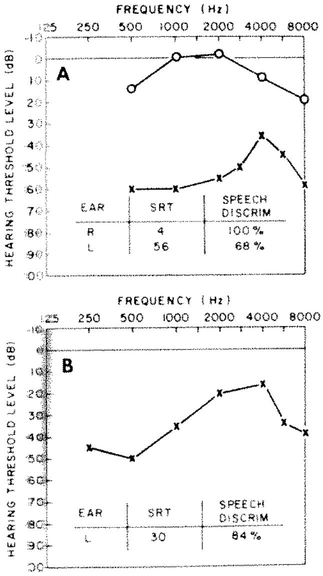


Fig. 3. (Case 2) Audiograms. A) At time of hospital admission; B) One month postoperative.

Case 3 An 11-year-old male developed ataxia, vertigo, nausea, and vomiting two days following a left-sided acute otitis media. He did not complain of difficulty hearing. The child had reportedly been hospitalized two years previously when similar symptoms of disequilibrium followed a left ear infection.

On examination, the child had an unsteady, wide based gait, no spontaneous nystagmus, and left-sided otitis media with effusion was observed with pneumatic otoscopy. Tympanocentesis of the left ear on the day of hospital admission yielded purulent liquid that was cultured and later grew *Staphylococcus aureus*, coagulase negative. Viral cultures from throat and stool specimens were negative. The boy was treated with oral ampicillin, and the symptoms subsided within three days.

Since this was the second episode of "labyrinthitis" associated with a left middle ear infection, it was postulated that there might be an abnormal communication between the middle and inner ear that was acting as a pathway for the spread of infection. Accordingly, the boy underwent further evaluation to uncover any findings that might substantiate the suspicion that a perilymph fistula was present in the left ear.

Audiometric tests revealed normal hearing in both ears, tympanometry indicated normal compliance for both eardrums, normal pressure in the right ear, and −150 mm H_2O pressure in the left ear. Electronystagmography revealed a right-beating direction-fixed

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positional nystagmus. During the fistula test, significant deviation of the eyes in the opposite direction was seen when positive pressure was applied in the left ear canal; however, no eye movement could be elicited with negative pressure in the left ear canal.

One month after the child had recovered from the left-sided otitis media he was readmitted and underwent a left exploratory tympanotomy. Although no leak of clear fluid was identified initially, following bilateral jugular vein compression with the patient in the Trendelenburg position clear fluid was seen to collect around the anterior edge of the stapes footplate. Adipose tissue obtained from the earlobe was packed in this region after the mucous membrane in the oval window niche had been abraded. Follow-up 14 months after surgery revealed that the boy still had normal hearing, and he had had no further episodes of disequilibrium or labyrinthitis.

COMMENT. There are numerous reports of children who have had recurrent bouts of meningitis and who have had exploratory tympanotomies that revealed an abnormal communication between the middle and inner ear.[1-5] This child may have had a variant of the same condition. That is, a microscopic fistula in the region of the anterior footplate most likely was a pathway for the ingress of pathogenic organisms, twice causing the symptoms of "labyrinthitis" associated with otitis media. If the fistula had not been repaired, it is conceivable that in the future this boy may have developed meningitis with a future episode of acute otitis media.

Case 4. A seven-year-old female rapidly developed bilateral progressively worsening sensorineural hearing loss. Annual school screening audiograms had indicated bilateral normal hearing for the two previous years. The only additional history thought to be relevant was that the girl's parents felt that their daughter's hearing loss began at the end of the summer when she had been swimming vigorously and learning to dive. Probably because of difficulty hearing her teacher and deterioration in the quality of her speech, she began to do poorly in school and became easily frustrated and angry.

Except for the hearing and language deficit, no abnormal physical findings were detected. A consulting neurologist found no abnormality except for the impairment of auditory function. The child did not fully cooperate during behavioral audiometric tests, but the results appeared to indicate a bilateral, moderately severe, sensorineural hearing loss. Results of brainstem auditory electric response (BSER) tests were consistent with these findings and the patterns were indicative of cochlear pathology. The child would not cooperate for ENG or posturography tests. Temporal bone polytomography revealed no specific abnormality.

An exploratory tympanotomy was performed on the right ear and a markedly abnormal round window niche with absent bony overhang and a completely visible round window membrane were found. At the inferior periphery of the round window membrane a defect could be seen through which clear fluid was flowing. The oval window and stapes footplate appeared to be normal. The opening in the round window membrane was repaired using adipose tissue from the earlobe.

Two days later, an exploratory tympanotomy was done on the left ear and the same anatomic abnormality was found but no obvious leak of clear fluid could be identified. Despite this, earlobe adipose tissue was placed against the readily visible left round window membrane.

Behavioral audiometric tests two months following surgery showed no change in hearing from preoperative levels. The girl has been rehabilitated with an appropriate hearing aid and she continues to attend regular classes at a public school.

COMMENT. Perilymph fistula in association with an anatomic variation similar to the one this child had has been reported.[6] Possibly the angle at which the round window membrane is situated with respect to the scala tympani may be related to the ability of the membrane to withstand force exerted by CSF pressure or rapid alterations in middle ear pressure.

Case 5. A seven-year-old male was lifting weights to "build up muscles" when he suddenly became unsteady, had difficulty standing, and felt an uncomfortable sensation in his right ear. Two days later the boy told his mother that he could not hear in his right ear, and he was immediately admitted to the hospital for evaluation. There was no otalgia or tinnitus. Copies of annual school screening audiograms indicated that he had had bilateral normal hearing as recently as seven months prior to this hospital admission.

On examination both ear canals and tympanic membranes were normal. The Weber test lateralized toward the left. A fistula test in the right ear was negative. The child was unsteady during the standard Romberg test and consistently fell toward the right during the tandem Romberg test. His gait was wide based and ataxic with eyes open, and with eyes closed he consistently veered toward the right. On positional testing, a few beats of left-directed nystagmus were noted when he was placed in the left-ear-down position, both with and without neck torsion.

An audiogram revealed normal hearing in the left ear and a profound hearing loss in the right ear. Tympanometry indicated normal middle ear pressure bilaterally.

Electronystagmography revealed a left direction-fixed nystagmus present throughout the tracing and persisting despite changes in position. Posturography was reported as showing a "peripheral vestibular pattern." Results of the complete blood count, urinalysis, erythrocyte sedimentation rate, fluorescent treponemal antibody test, cold agglutinin titers, and blood coagulation studies were all normal. Temporal bone polytomography, including a 20° oblique view to examine the cochlear aqueducts, revealed no specific abnormality.

Three days following hospital admission an exploratory tympanotomy was performed on the right ear. An air bubble trapped within a collection of clear fluid could be seen at the round window niche. Clear fluid persistently recollected at this site after gentle suctioning. The stapes superstructure and footplate were normal. Adipose tissue obtained from the earlobe was placed in both the oval and round window niches. After surgery, the vertiginous symptoms abated, but there was no return of hearing in the right ear when the boy was tested three months following repair of the fistula.

COMMENT. Compared with the other cases, this child had the most obvious association between excessive exertion and the rapid onset of hearing loss. Also, since this child was the one who presented after the other four children, he probably had a more optimal evaluation. The normal results of hematologic and serologic tests were helpful in lessening the suspicion that the hearing loss was a result of viral infection or a hypercoagulable state with vascular occlusion. The position-induced nystagmus that was initially seen may have been significant in that other authors have found tests of vestibular function to be important in detecting the presence of a perilymph fistula.[7,8]

DISCUSSION

PRIOR EVIDENCE THAT PERILYMPH FISTULAE OCCUR IN CHILDREN

The preceding case reports serve to illustrate that hearing loss of rapid onset, as well as symptoms of disequilibrium in children, may be associated with an identifiable perilymph fistula. The concept that such fistulae can occur in the pediatric age group is not entirely new. Over the past several years, there have been numerous reports of abnormal communications between the inner and middle ear associated with recurrent bouts of meningitis in children.[9-14] It has been postulated that the fistulae provide a pathway for the spread of infection from the middle ear, toward the subarachnoid area, and into the meninges. In some children who had experienced recurrent meningitis, an unmistakable opening, presumed to be a congenital fistula, was identified in the stapes footplate.

It is now known that perilymph fistulae can be found in young patients who have not had meningitis. Although there have been no previous reports specifically showing a relationship between sudden physical exertion or barotrauma and perilymph fistula in children, sporadic reports which have appeared seem to indicate that such a relationship may exist. In 1970, Stroud and Calcaterra[15] reported four cases of perilymph fistula, one of whom was a seven-year-old girl who reportedly developed the fistula while she was laughing vigorously. In 1972, Farrior and Endicott[16] described six cases of "congenital mixed deafness" two of whom were under 15 years of age. Four of the patients had a profuse gush of perilymph fluid when stapedectomy was done; one had a stapes that virtually "exploded" into the middle ear when mucous membrane blisters surrounding the stapes were punctured, and one had an obvious leak of fluid from around the edge of the oval window. The authors theorized that increased CSF pressure transmitted through a patent cochlear aqueduct caused what they termed "perilabyrinthine hydrops." They explained that the fluctuating sensorineural hearing loss results from increased perilymph fluid pressure inside the inner ear, and the low-tone conductive hearing loss results from the outward impaction and fixation of the stapes in the overhanging lip of the oval window. In 1973, Goodhill et al reported 18 cases of sudden deafness with rupture of the labyrinthine window membranes, 2 of whom were children – one an 11-year-old male, the other a 15-year-old female. Both children had a history of sudden physical exertion associated with the onset of the hearing loss. The following year, in 1974, Arenberg and Stroud[18] published a report of a nontraumatic, spontaneous perilymph fistula which caused symptoms similar to Ménière's disease in a 10-year-old female.

More recently, Pashley and Shapiro[19] reported the case of a spontaneously occurring oval window perilymph fistula in a 12-year-old male who had a congenital malformation of the stapes and an abnormally wide cochlear aqueduct. Knight[20] reported on eight carefully selected children who had fluctuating or profound sensorineural hearing loss and who underwent exploratory tympanotomy; five were found to have perilymph fistulae, one had a congenital deformity of the middle ear (presumably without a fistula), and in one the round window membrane could not be seen but there was no evidence of perilymph leakage.

In addition to alternobaric factors[21] involved in the development of perilymph fistulae, blunt trauma to the head reportedly can be associated with the development of such fistulae. In 1978, Healy et al[22] reported the case of a five-year-old male who developed ataxia, episodic vertigo, and severe left-sided hearing loss with intermittent tinnitus eight days after a head injury. At the time of the exploratory tympanotomy, perilymph could be seen escaping from the anterior portion of the oval window.

PATHOGENESIS AND THEORETICAL CONSIDERATIONS

Although reports of the occurrence of perilymph fistulae have increased in number, the pathogenesis of this otologic disorder is not yet entirely understood. It is generally accepted that rupture of the labyrinthine window membrane may be the result of rapid alterations in perilymphatic fluid pressure. Presumably, if the cochlear aqueduct is patent, then alterations in CSF pressure can be transmitted via the aqueduct to the inner ear compartment containing perilymph. Goodhill et al[17] described both explosive and implosive routes for the transmission of a deleterious force to the inner ear. In the explosive route, a force (due to physical exertion) from increased CSF pressure is transmitted from the subarachnoid space via the cochlear aqueduct, or the laminae cribrosae of the internal auditory meatus, into the inner ear compartment containing perilymph. On the other hand, the implosive route involves a force (barotrauma) from sudden alteration in middle ear pressure acting directly on the middle ear side of the round window membrane or at the annular ligament of the oval window, or both.

Certainly, both of these routes for the transmission of a damaging fluid pressure are understandable. However, in an attempt to understand the pathogenesis of symptomatic perilymph fistulae, the question arises as to why certain individuals should be susceptible to the otologic disorder while others are not. An answer to this may come from an analysis of relevant anatomic factors. When the cochlear aqueduct is patent, then fluctuations in CSF pressure can be more readily transmitted to the inner ear, and if the cochlear aqueduct is widely patent, the delicate inner ear structures can more easily be damaged by rapid, wide fluctuations in perilymphatic fluid pressure. For a long time controversy has existed as to the patency of the human cochlear aqueduct. Wtodyka[23] has recently reported results of a study of the patency of the cochlear aqueduct in 250 human temporal bones. He found that "the disappearance of patency of the cochlear aqueduct is a progressive phenomenon reflecting the biological process of aging in the organism . . . the aqueduct was patent in 75% of cases under 21 years of age, but (in) only 32% of the elderly." In view of this, the inner ears of children may be more subject to damage from rapid alterations in perilymph pressure due to changes in CSF pressure than the inner ears of adults.

Other anatomic factors may also be important. Parisier and Birken[13] reviewed the causes of recurrent meningitis due to a spontaneous oval window fistula and they found that most of the affected individuals had an underlying congenital anomaly of the middle or inner ear, or both. Further, they reported that radiographic examinations in several patients demonstrated a shortened cochlear coil, a dilated semicircular canal system, and a widened inner ear vestibule. Pullen[6] detected a common anatomic variation in the cases of round window membrane rupture that he reported. He found the position of the round window membrane to be abnormal – it was "visible and angled less than one would normally expect." Goodman and Morioka[24] reported finding an abnormally large round window niche and membrane in a 19-year-old male with a ruptured round window membrane. Other authors[4,14,25] have described temporal bone anomalies and otic capsule CSF or perilymph fistulae in children with Klippel-Feil syndrome, Pendred's syndrome, craniosynostosis, and Mondini dysplasia.

Thus, it would seem that inherent anatomic variations in certain individuals may predispose them to the development of labyrinthine membrane rupture. However, rupture of a labyrinthine membrane itself may not entirely explain the symptoms of persistent or fluctuating hearing loss that can be seen in patients who are found at exploratory tympanotomy to have a perilymph fistula. Weisskopf et al,[26] in experimental studies on guinea pigs, have shown that within the limitations of single-electrode cochlear microphonic recording, there is only slight sensorineural hearing loss when the round window membrane is ruptured. In view of this, the mechanism involved in the development of hearing loss associated with perilymph fistula may be complex. Goodhill[27] and Simmons[8] offered theoretical explanations. They postulated that rupture of a labyrinthine window membrane may, in turn, cause excessive pressure to be exerted on such inner ear structures as Reissner's membrane, the basilar membrane, or the tectorial membrane. If the pressure is exerted rapidly enough and is of great enough magnitude, then rupture of an intracochlear membrane might occur with a chance for mixture of perilymph and endolymph. If this were to occur, then the associated hearing loss may be due partly to actual tissue injury at the site of the break and partly to the mixture of fluids extending into regions of the cochlea distant to where the membrane was ruptured.

TABLE 1. CLASSIFICATION OF PERILYMPH FISTULAE

- Congenital — communication between inner and middle ear is present at birth
  - Without associated temporal bone or extracranial abnormalities, e.g., isolated stapes footplate fistula
  - With associated temporal bone or extracranial abnormalities, e.g., Mondini dysplasia, Klippel-Feil syndrome, Pendred's syndrome, craniosynostosis, widely patent cochlear aqueduct
- Acquired — normal ear anatomy at birth
  - Iatrogenic — poststapedectomy
  - Traumatic
    - Direct — penetrating wound in the ear
    - Indirect — blunt injury to the head
    - Barotrauma
      - Implosive — alternation in tubotympanic pressure
      - Explosive — alteration in CSF pressure
  - Erosion of bone
    - Luetic
    - Cholesteatoma
    - Neoplasm
- Combined — underlying anatomic abnormality that makes the ear susceptible to injury from alterations in pressure in perilymphatic fluid or middle ear, or both.

Once intracochlear or labyrinthine window rupture, or both, have occurred, healing may proceed in different ways. Fluid dynamics and pressure relationships within the inner ear are such that healing of an intracochlear membrane rupture may depend upon prior sealing of the round or oval window membrane rupture. Or, the intracochlear membrane rupture may heal regardless of a persistent leak of fluid at the round or oval window. The importance of this is that the hearing loss associated with an identifiable labyrinthine window perilymph fistula likely reflects intracochlear events. In fact, Simmons[8] reported finding discrete hearing deficits at narrow bands of frequency in the audiograms of several patients who were found to have rupture of a labyrinthine membrane. Hearing thresholds were measured at 100 Hz increments between 400 and 1300 Hz. One patient exhibited a 20 dB "hole" at 600 Hz and a decreased ability to discriminate pitch between 500 and 700 Hz. Theoretically, this type of limited hearing loss can be correlated with a site along the basilar membrane where rupture and tissue injury occurred.

CLASSIFICATION

Based on our own experience and

that of others who have reported cases, the classification of types of perilymph fistula is proposed in Table I.

WHEN TO SUSPECT A PERILYMPH FISTULA

It has always been difficult to find a tenable pathophysiologic explanation for unilateral sensorineural hearing loss in children. Viral, bacterial, vascular, and hereditary factors have classically been considered as being causal. It is interesting to note that in the case of meningitis secondary to a fistula of the stapes footplate reported by Stool et al,[2] the child's previous unilateral hearing loss had been attributed to mumps. It is now apparent that perilymph fistula must be considered along with other etiologies when a child presents with unilateral sensorineural hearing loss, or symptoms of disequilibrium, or both. When evaluating a child with rapid onset or fluctuating sensorineural hearing loss, the following factors should make one suspect the presence of a perilymph fistula.

1. History of antecedent sudden physical exertion, barotrauma, or head injury.

2. Recurrent bouts of labyrinthitis, meningitis, or both.

3. Known temporal bone, cranial, or extracranial skeletal anomalies.

4. Objective evidence of a persistent vestibular disturbance when other etiologic factors have been eliminated.

DIAGNOSTIC AIDS

At present, there is no single test or combination of tests that is diagnostic of a perilymph fistula. However, the following is a summary of the diagnostic procedures that may be of value in determining the likelihood of a perilymph fistula being present.

Assessment of Hearing. Serial audiograms should be obtained to document the fluctuating, progressively worsening, or stable character of the sensorineural hearing loss. If the hearing loss is of rapid onset, it is advisable to obtain daily or alternate-day audiograms for seven to ten days, or until a decision is made to explore the middle ear

When hearing appears to be normal with routine pure-tone testing, yet there are other reasons to suspect a fistula, then it is worthwhile to obtain an audiogram with 100 Hz increment pure-tone testing from 400 to 1300 Hz. This is where a "hole" (q.v. Pathogenesis and Theoretical Considerations) in the audiogram can be present presumably due to rupture of an intracochlear membrane which has occurred along with rupture of a labyrinthine window membrane. Eggermont et al[28] described a technique that may be helpful for evaluating localized basilar membrane deficiencies in children. Specifically, the technique involves the derivation of VIII nerve action potentials from regions of the basilar membrane by using high-pass filtered noise and advanced computer processing.

Observe the configuration of the pure-tone audiogram. Low-tone hearing impairment with inordinately good speech discrimination ability may be indicative of stiffness of the inner ear structures, or an abnormal fluid pressure within the inner ear.[29]

When younger children are unable or unwilling to cooperate during behavioral audiometric testing, information concerning the integrity of the auditory pathways should be obtained by BSER testing.

Fistula Test. This is performed by using a Brunning otoscope or Politzer bag to exert first positive, then negative pressure against the eardrum while the eyes are observed for corresponding deviation. The response may be brief, coming only with the initial stimulus. When the test is positive there is usually a startle reaction with a quick movement of the head away from the side where the pressure is being applied. Use of Frenzel glasses is helpful in suppressing visual fixation, and performing the test with ENG leads attached enables graphic recording of the response.

Positional Testing. If the child is able to cooperate, the Nylen-Bárány maneuver should be utilized. Experience with the use of this test in adults indicates that subjects who were later found to have an identifiable perilymph fistula most often exhibited a typical peripheral vestibular response;[7] that is, there was rotary nystagmus when the affected ear was placed downward, with a noticeable latency before onset. It was associated with subjective vertigo, and the response fatigued within 30 seconds. Upon resuming the sitting position, a similar response occurs with reversal in the direction of nystagmus. The response diminishes with repeated positional maneuvers. It is helpful to do the positional testing as part of a complete ENG so that a graphic recording of responses can be reviewed and analyzed.

Evidence of Vestibular Ataxia. The standard Romberg and tandem Romberg tests are used to elicit vestibular ataxia. Posturography, more properly termed the vestibulospinal stability test[30,31] is a new method of testing the vestibulospinal system stability. This method is well suited for children because the procedure takes only two minutes to complete and requires only that the child stand upright on the platform.

Gait Testing. Gait is observed both with the subject's eyes open and with them closed. In this way, vestibular ataxia can be differentiated from cerebellar ataxia; the former is exacerbated with eyes closed, while the latter is not much influenced. Some assessment must be made of the integrity of the proprioceptive sense to eliminate the possibility that impairment in this system is the primary cause for elicited ataxia.

Temporal Bone Polytomography. Tomograms are obtained in order to visualize the cochlear aqueduct and to identify a possible abnormality of the middle ear, bony labyrinth, internal auditory canal, or the canal for the facial nerve. Optimal views for visualization of the cochlear aqueduct are the coronal, the 37° oblique,[32] or the 20° oblique.[33] In the normal ear, the distal end (near the jugular bulb) of the cochlear aqueduct can always be visualized, but the proximal portion (near the hook portion of the cochlea) is only rarely seen. Therefore, with polytomography, lack of visualization of the cochlear aqueduct except for its distal aperture is of no clinical significance while a noticeable widening of the proximal portion appears to be highly significant. A posterior fossa contrast study can be helpful in demonstrating the presence of a fistula between the area cribrosa of the internal auditory meatus and the vestibule,[34] but in most cases the contrast study is not of sufficient value to warrant its use, especially in children.

MANAGEMENT

Since the presence of perilymph fistulae in children has only recently been recognized, there are no clear guidelines for management. However, the summary of a therapeutic regimen that seems to be appropriate follows.

1. The patient should be admitted to the hospital, placed at bedrest with the head elevated, be observed, and undergo diagnostic studies.

2. It is helpful to find audiometric, vestibular, and radiographic evidence that is consistent with the presence of a perilymph fistula. However, if the results of diagnostic studies are equivocal and there is a history that clearly links barotrauma or strenuous physical exertion with the onset of symptoms, then exploratory tympanotomy should still be considered. When the history is strongly suggestive of perilymph fistula and there is a persistent vestibular disturbance, progressively worsening hearing, or both, then exploratory tympanotomy is warranted. The timing of surgical intervention is controversial. Simmons et al[35] have stated that many perilymph fistulae heal spontaneously with good return of hearing, and he suggests waiting seven to ten days before proceeding with an exploratory tympanotomy. In fact, based on his theory that an intracochlear membrane rupture may result from rupture of a labyrinthine window membrane, he speculates that early closure of the window membrane rupture may interfere with healing of the intracochlear membrane rupture. On the other hand, if progressive hearing loss is detected on serial audiograms, probably surgical exploration is warranted. The slope of the audiometric pattern may be helpful in deciding if and when

to explore an ear for sudden hearing loss. Down-sloped patterns generally are correlated with a poor prognosis for spontaneous recovery, while up-sloped patterns are correlated with a better prognosis for spontaneous recovery.

3. If no fistula is evident at exploratory tympanotomy, an attempt to elicit evidence of one should be made by placing the patient in the Trendelenburg position and using bilateral jugular vein compression. In older children, the tympanotomy can be done under local anesthesia, and the child can be requested to do a Valsalva's maneuver.

4. Abrade or partially remove mucous membrane from around the site of the fistula and use earlobe adipose or vein graft to repair the fistula.

CONCLUSION

There is now enough evidence to conclude that sudden hearing loss, or disequilibrium, or both can be caused by a perilymph fistula in adults. In this report, five cases of perilymph fistulae in children are presented, four of whom had histories suggesting that physical exertion or barotrauma was a contributing causal factor. Thus, it appears that children as well as adults are susceptible to developing perilymph fistulae. In fact, congenital abnormalities and widely patent cochlear aqueducts may render children more susceptible than adults to developing this otologic disorder.

Since there is no single test or combination of tests that can prove the presence of a perilymph fistula, the ultimate diagnosis must be made at exploratory tympanotomy. However, in our experience, identifying and repairing the fistula did not result in sustained hearing improvement. This presents a problem; although it is now apparent that perilymph fistulae in children may be associated with impairment of auditory and vestibular function, otologic surgery to confirm the presence of and repair the fistula may not improve impaired hearing. There is a need to develop an appropriate *noninvasive* diagnostic test, and to investigate further the pathogenesis of intracochlear events occurring in association with perilymph fistulae.

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SECOND SYMPOSIUM
NEUROLOGICAL SURGERY OF THE EAR

Attention has been called to the fact that an incorrect date has been published in other journals. Please be aware that the date of the Second Symposium on Neurological Surgery of the Ear is February 3-8, 1979 in Sarasota Florida.

Ann Otol 87:1978

FACIAL NERVE REPAIR IN CEREBELLOPONTINE ANGLE SURGERY

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Facial nerve continuity was restored during cerebellopontine angle tumor removal in nine cases. The distal facial nerve was rerouted from the stylomastoid foramen into the cerebellopontine angle. Direct suture was accomplished in seven cases while two required interposition of a greater auricular nerve graft. There was excellent return of facial function in eight of the nine cases. Overall results are superior to nerve substitution techniques. The facial nerve should be inspected for continuity following tumor removal. If one is not certain the nerve is intact, the proximal facial stump should be identified at the brain stem and facial nerve continuity reestablished. A nerve substitution procedure should be resorted to at a later time only when the proximal facial stump is not identifiable.

Disruption of continuity of the facial nerve in the cerebellopontine angle is an inevitable consequence of tumor removal in this area in some cases. The disfiguring disability resulting from facial paralysis has usually been treated by a nerve substitution procedure. A facial-hypoglossal anastomosis at a later date has been our procedure of choice.

This paper deals with a different approach to the problem: restoration of continuity of the facial nerve. Techniques of restoring facial nerve continuity in the cerebellopontine angle are described. We present nine cases and compare the results with facial-hypoglossal nerve anastomosis.

FACIAL NERVE INJURY

Despite the most careful microsurgical technique, disruption of facial nerve continuity may occur during the course of cerebellopontine angle tumor removal. The likelihood of this complication depends on the type of tumor: acoustic neurinoma, facial nerve neurinoma, meningioma, and cholesteatoma.

Acoustic Neurinomas. Acoustic neurinomas are the most common tumor of the cerebellopontine angle. In a series of 500 accoustic tumors treated at the Otologic Medical Group, Inc., between 1968 and 1975, the facial nerve was preserved in 96.6% of cases.[1] This excellent record of facial nerve preservation is made possible by microsurgical techniques and the translabyrinthine approach. With this approach the surgeon is able to identify the facial nerve as it exits the internal auditory canal, a landmark which remains constant regardless of the degree of distortion of the facial nerve by a large tumor in the angle.

Despite the most careful technique, however, the facial nerve will be disrupted in some cases. Large tumors may thin the nerve to a ribbonlike band at the porus acusticus, the point where the tumor is most adherent to the nerve.

At times the facial nerve appears to be invaded by tumor. We encounter this most often in von Recklinghausen's disease which is characterized by tumors which are particularly invasive.

Facial Nerve Neurinomas. Facial nerve neurinomas may be totally within the temporal bone. The techniques of removal and restoration of facial nerve continuity in these cases have been well described.[2]

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In some cases the tumor arises within the temporal bone and extends into the internal auditory canal without facial paralysis; initial symptoms resemble those of acoustic neurinomas. X-rays often reveal bone destruction in the area of the geniculate ganglion. This finding suggests this variant of facial nerve neurinoma.

At times facial nerve neurinomas arise within the internal auditory canal or the cerebellopontine angle. The symptoms in these cases are identical to those produced by an acoustic tumor, and preoperative differentiation is usually not possible.

Facial nerve signs (weakness or twitching) often are absent even with relatively large tumors. As a result it is rare to discover a small facial nerve neurinoma. Tumor removal usually requires removal of the involved segment of the nerve.

Meningiomas. Meningiomas are the second most common lesion in the cerebellopontine angle. These tumors usually arise from the petrous ridge anterior to the internal auditory canal and displace the facial nerve posteriorly. The nerve is very susceptible to injury.

We prefer to remove a meningioma by the transcochlear approach.[3] Meningiomas usually may be differentiated from other cerebellopontine angle tumors by their increased density on computerized axial tomography and marked enhancement with iodine injection.

In the transcochlear approach we remove the facial nerve from the fallopian canal and displace it posteriorly. Although tumor removal and facial nerve preservation are facilitated with this new approach, meningiomas often invade the facial nerve and the facial nerve must be sacrificed. This was the case in five of ten meningiomas recently operated.[4]

Cholesteatomas. Primary cholesteatomas of the cerebellopontine angle present a special problem in facial nerve preservation. These tumors envelop the nerves in the angle; total removal of the matrix is difficult without injuring them.

TECHNIQUE OF FACIAL NERVE REPAIR

When the facial nerve is severed during tumor removal, rehabilitation is best accomplished by restoration of its continuity.

There are three steps in the technique: 1) identification of the nerve stump at the brain stem, 2) rerouting of the distal facial nerve, and 3) direct anastomosis or interposition of a nerve graft.

Identification of Proximal Nerve. There is little problem in identifying the proximal nerve stump in cases of facial nerve neurinomas and in smaller acoustic tumors.

In the case of a large acoustic tumor, the facial nerve may be involved near the brain stem, and identification of the stump may be quite difficult. The VIII nerve is also involved with tumor in these cases and cannot be used as a landmark to direct one to the facial nerve.

Figure 1 shows the anatomy of the cranial nerves at the brain stem. The facial nerve originates from the brain stem medial and slightly caudad to the acoustic nerve. If this landmark is destroyed, find the origin of the IX cranial nerve by tracing it from the jugular foramen to the brain stem. The facial originates approximately 4 mm cephalad and 2 mm medial to the origin of the IX nerve. In most cases one is able to identify a stump of nerve of sufficient length to anastomose to the distal nerve. Only in those cases where the nerve cannot be identified at the brain stem is a nerve substitution procedure indicated later.

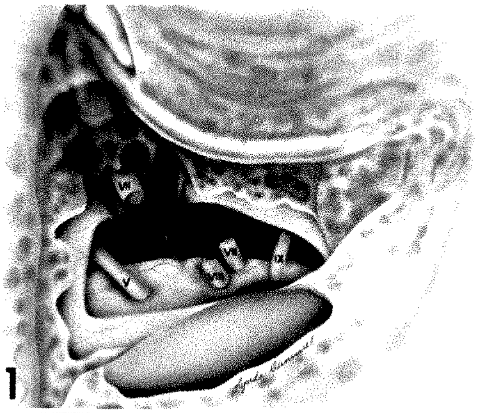
Rerouting the Distal Nerve. Rerouting the distal facial nerve requires bone removal from two thirds of the circumference of the fallopian canal from the internal auditory canal to the stylomastoid foramen. This is done to gain extra length of nerve. This dissection is easier than it might otherwise be because of prior labyrinthine bone removal (Fig. 2).

After bone removal is completed, the greater superficial petrosal nerve is severed to free the geniculate ganglion, and the chorda tympani nerve is transsected. The nerve is then removed from its canal and placed directly into the cerebellopontine angle.

Nerve Suture. A direct end-to-end anastomosis of the nerve is possible if there is a sufficiently long stump at the brain stem (Fig. 3).

The intracranial portion of the facial nerve is devoid of epineurium and is very fragile. The most one can hope to accomplish is a single through-and-through suture to stabilize the anastomosis. Even this is difficult deep in the cerebellopontine angle with pulsations of both the brain stem and the proximal nerve stump with each heart beat.

Monofilament suture (7-0) is used. It is passed through the nerve without lateral tension, or it may tear out of the nerve. After the proximal suture is placed, the needle is



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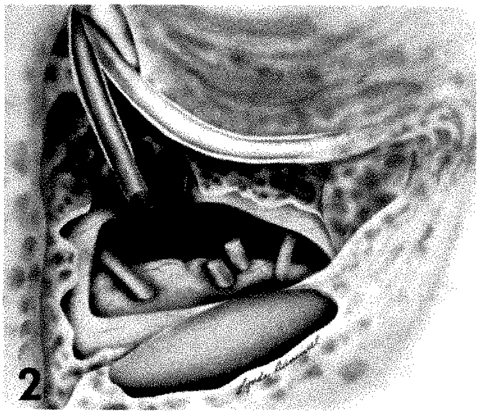

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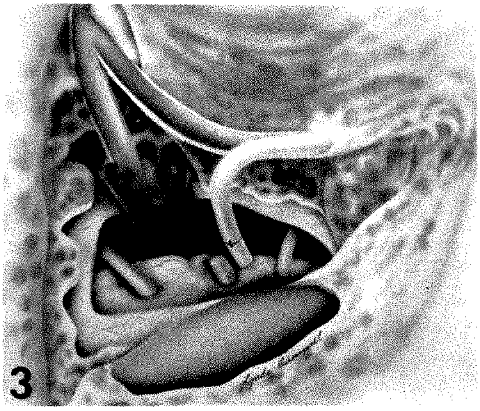

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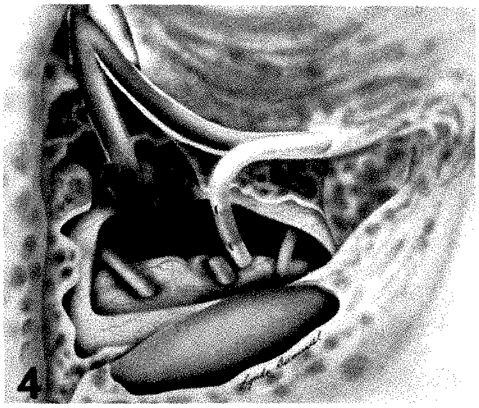

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Fig. 1. The brain stem is exposed by the translabyrinthine approach. The tumor has been removed and the facial nerve severed. The stump of the facial nerve arises slightly medial and caudal to the acoustic nerve and medial and cephalad to the IX nerve.

Fig. 2. The bone of the fallopian canal is removed from two thirds of the circumference of the facial nerve.

Fig. 3. The rerouted facial nerve is anastomosed to the facial nerve stump near the brain stem.

Fig. 4. A greater auricular nerve graft has been interposed.

passed through the distal nerve. The epineurium of the distal nerve is trimmed back slightly to expose the axons. The segments are carefully approximated until they are just contacting and the suture is tied. If tied too tightly, the suture will be pulled from the proximal nerve. Fine alligator forceps are best for placing and for tying this suture.

If the nerve ends will not approximate without tension, the interposition of a nerve graft is necessary. The greater auricular nerve is used. The epineurium is trimmed slightly before the sutures are placed. The proximal anastomosis is accomplished first as has just been described. The distal anastomosis is then completed. This is usually more easily performed because of the superficial locale of the anastomosis and the lack of transmitted pulsations (Fig. 4).

After the anatomosis has been completed, abdominal fat is used to obliterate the mastoid cavity. Care is taken to position pieces of the fat so that they support the anastomosis or graft and do not produce tension.

CASE SUMMARIES

Nine patients have had restoration of facial nerve continuity in the cerebellopontine angle following tumor removal. Six of these had an acoustic neurinoma; two had a facial nerve neurinoma; and one patient had both a facial nerve neurinoma and an acoustic neurinoma.

Direct end-to-end anastomosis was accomplished in seven patients. In two patients a greater auricular nerve graft was interposed. Facial nerve function

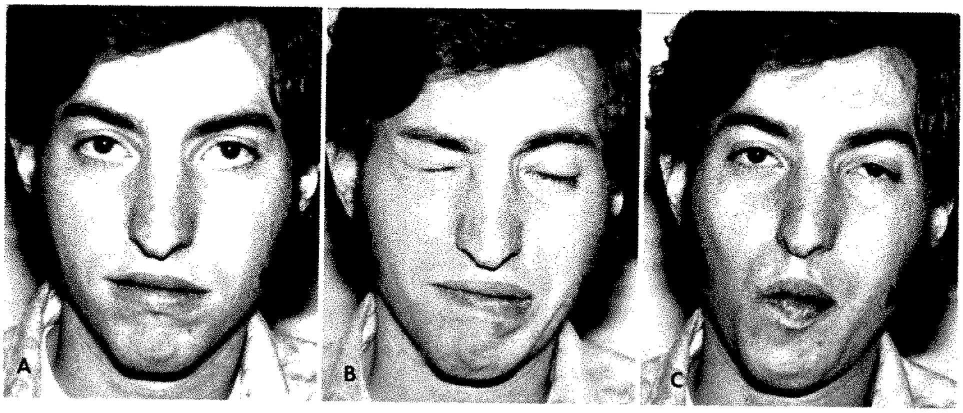

Fig. 5. A) B) C) (Case 1) This patient had a nerve graft following excision of a facial nerve neurinoma two years previously. Note near normal resting tone with good eye closure and mouth movement.

began to return as early as six months postoperatively and has continued to improve for three or more years postoperatively.

Of the nine patients who have undergone this procedure, eight have had an excellent result. One patient had no return of facial function, and it is assumed that the anastomosis did not remain intact.

Near normal resting tone has been achieved in the eight patients who also have voluntary facial motion. As would be expected, all patients have mass motion. There is no appreciable difference in the six patients with direct anastomosis and the two who had nerve grafts.

Details of the findings are recorded below. Four of the nine cases were operated by other members of our group.

CASE REPORTS

Case 1. A 21-year-old male had a sudden loss of hearing, without vertigo, eight months prior to being seen. There was some minor intermittent facial twitching. Otologic examination was normal. The SRT was 30 dB with 56% speech discrimination. Petrous pyramid x-rays detailed an enlarged internal auditory canal. The acoustic reflex decayed, and the ENG showed a 31% reduction in vestibular response. Pantopaque® study outlined a 3 cm filling defect in the left cerebellopontine angle.

Because of the history of facial twitching, a facial nerve neurinoma was suspected. A 3 cm tumor was removed by the translabyrinthine approach. A small stump of the facial nerve was identified at the brain stem. The rerouted distal facial nerve would not approximate, so a greater auricular nerve graft was placed. Within six months the patient had some return of facial function. Two years later he has an excellent result with normal tone, good eye closure, and good voluntary motion (Fig. 5 A, B and C).

Case 2. A 57-year-old female had had progressive loss of hearing, without vertigo, in the right ear for 20 years. Otologic examination was normal. There was an 80 dB speech awareness threshold with no speech discrimination. The ENG showed a total loss of vestibular function in the right ear. Posterior fossa myelography outlined a 2 cm mass.

The tumor was removed via the translabyrinthine approach. It surrounded the facial nerve which was divided and reanastomosed. Six years postoperatively the patient has an excellent return of facial function.

Case 3. A 61-year-old male had had progressive hearing impairment, without vertigo, in the left ear for four years. There was associated tinnitus. The otologic examination was normal. There was a 70 dB hearing impairment with 84% speech discrimination. Petrous pyramid x-rays showed an enlarged canal. There was a 74% reduction of vestibular response on the left side. Pantopaque® outlined a 1.5 cm filling defect in the cerebellopontine angle.

The neurinoma was removed via the translabyrinthine approach. A segment of the facial nerve was intimately involved by the tumor and excised with it. An end-to-end anastomosis of the nerve was accomplished at the porus acusticus. Four years postoperatively the patient has an excellent return of facial function.

Case 4. A 35-year-old patient had had a progressive hearing impairment in the left ear for three years. He also had unsteadiness and tinnitus. The otologic examination was normal. There was a 20 dB hearing impair-

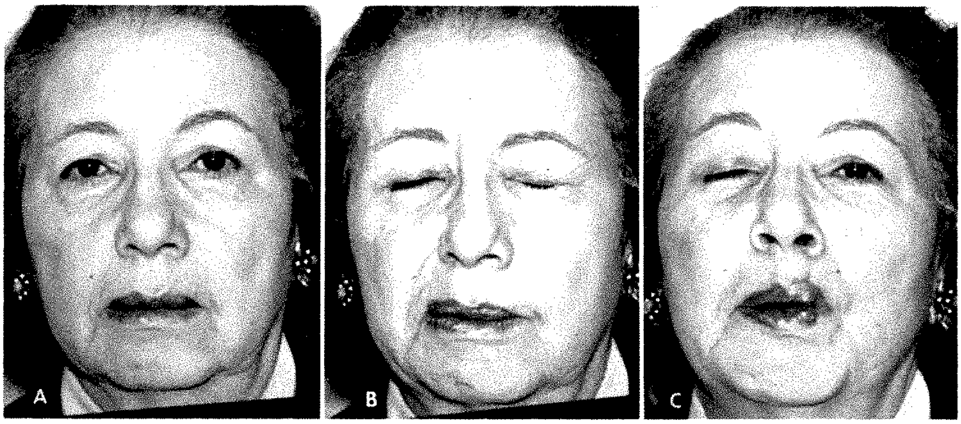

Fig. 6. A) B) C) (Case 7) A nerve graft was placed following facial nerve neurinoma removal two years previously in this 65-year-old female.

ment with 96% speech discrimination. X-rays showed an enlargement of the internal auditory canal. The ENG was normal. Pantopaque® outlined a 3 cm neurinoma on the left side.

The tumor was totally removed by the translabyrinthine approach. The facial nerve was divided during the tumor removal. It was sutured directly in the angle. Seven years postoperatively the patient has an excellent return of facial function.

Case 5. A 30-year-old patient had had a progressive loss of hearing in the right ear for three years. He also had tinnitus, but no dizziness. On physical examination there was decreased sensation over the right side of the face. The internal auditory canal was enlarged on the right. The vestibular response was reduced 100% on that side, and a 3 cm filling defect was outline by Pantopaque®.

An acoustic neurinoma was removed by the translabyrinthine approach. The tumor invaded the facial nerve which was divided near the brain stem. The distal nerve was rerouted and anastomosed at the brain stem. Three years postoperatively the patient has an excellent return of facial function.

Case 6. A 60-year-old female had had progressive loss of hearing in the left ear for five years. She also complained of intermittent tinnitus, dizziness, and spasms of the left facial musculature. Her otologic examination was normal. There was total loss of hearing in the left ear. Petrous pyramid x-rays revealed an enlargement of the left internal auditory canal. The vestibular response was reduced 67% on the left side. Pantopaque® outlined a 3 cm filling defect in the cerebellopontine angle.

At translabyrinthine surgery a large neurinoma was encountered. It invaded the facial nerve, and, in fact, may have arisen from the facial nerve. A segment of the facial nerve was removed with the tumor. The distal facial nerve was then rerouted and a direct anastomosis accomplished. Three years postoperatively the patient has a good return of facial function.

Case 7. A 65-year-old patient had had a progressive loss of hearing and tinnitus in the right ear for two years. Her otologic examination was normal. There was a 40 dB speech awareness in the right ear with no understanding. The right internal auditory canal was enlarged on petrous pyramid x-rays. There was a 77% reduction of the vestibular response on ENG. Pantopaque® outlined a 2 cm filling defect in the left cerebellopontine angle.

At translabyrinthine surgery a neurinoma was found originating from the facial nerve. A total removal of the tumor was accomplished, and when the rerouted distal facial nerve would not approximate the nerve stump, a greater auricular nerve graft was placed. Two years postoperatively the patient has an excellent return of facial function (Fig. 6 A, B and C).

Case 8. A 28-year-old male complained of difficulty hearing on the telephone for two years. He also complained of tinnitus, but no dizziness. His otologic examination was normal. There was a 20 dB hearing impairment in the right ear with 100% discrimination. Because of the slight hearing impairment and unilateral tinnitus, a neuro-otologic evaluation was obtained. There was enlargement of the right internal auditory canal and a 60% reduction of vestibular response on ENG. Pantopaque® outlined two filling defects in the cerebellopontine angle; one, 2 cm in diameter, and the second, 1.5 cm in diameter.

At translabyrinthine surgery a 1.5 cm neurinoma was found arising from the inferior vestibular nerve. A second 2 cm neurinoma arose from the facial nerve and invaded the trigeminal nerve. Both tumors were removed. The rerouted facial nerve was directly anastomosed to the nerve stump at the brain stem. Five years postoperatively the patient has an excellent return of facial function.

Case 9. A 41-year-old patient had had a progressive hearing impairment of one year's duration. There were no other symptoms. On otologic examination there was a decreased facial sensation on the left side. There was also early papilledema and a total loss of hearing in the left ear. The internal auditory canal was enlarged on that side, and there was a 100% loss of vestibular function.

A 4 cm neurinoma was removed via the translabyrinthine approach. The facial nerve was severed near the brain stem. A direct anastomosis was accomplished. Seven years postoperatively the patient has no return of facial function.

DISCUSSION

For many years our group has used the facial-hypoglossal nerve substitution technique. The results with this technique are generally quite satisfactory. Good resting tone is usually achieved. Variable degrees of voluntary motion are obtained, but mass motion is always present. Facial motion usually does not accompany emotional expression. At times involuntary facial motion with speaking is bothersome. Rarely does tongue denervation cause a problem.

We feel that overall results with facial-facial anastomosis are superior to those obtained with facial-hypoglossal anastomosis. Tone is generally better as is voluntary movement. Facial motion is appropriate with emotion; this is an advantage over facial-hypoglossal anastomosis. Synkinesis is still present, but involuntary motion with speaking does not occur. The morbidity of tongue denervation, though minor, is avoided.

A further advantage of this procedure is that it is performed at the time of tumor removal so that the period of disability is shortened. The facial-XII anastomosis is usually delayed several months to allow recovery from the primary surgery. It is better not to create the added disability of tongue denervation with attendant early swallowing problems in these patients, many of whom had large tumors and may be quite ill.

CONCLUSION

Because restoration of facial nerve continuity is superior to a nerve substitution procedure, the facial nerve should be inspected to insure continuity in all cases following cerebellopontine angle tumor removal. It is often difficult to ascertain if the facial nerve is intact following tumor removal. Despite the surgeon's judgment that the facial nerve was intact in 96.6% of our series, 13.5% of patients had poor recovery of facial function following removal of a medium or large tumor. Either the surgeon's judgment regarding nerve continuity was incorrect, or the nerve was not viable because of loss of its blood supply or due to scarring in the cerebellopontine angle.

If one cannot be absolutely sure that the facial nerve is intact, an attempt should be made to identify the proximal facial nerve stump at the brain stem. In most cases sufficient nerve will remain to achieve restoration of facial nerve continuity.

In those cases where the nerve is destroyed at the brain stem, a delayed VII-XII anastomosis is recommended.

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OTOSCLEROSIS: VESTIBULAR SYMPTOMS AND SENSORINEURAL HEARING LOSS

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Of 546 patients with otosclerosis, 500 who had not had ear surgery were divided into four groups according to the relative and absolute amounts of sensorineural hearing loss in the hearing-impaired ears. The first three groups of patients had progressively less of a conductive component and progressively more of a sensorineural component to their hearing losses. The fourth group of patients had pure sensorineural hearing impairments. The remaining 46 patients were placed in group V. They had bilateral hearing losses and had had a prior unilateral stapedectomy for otosclerosis and they had received medical therapy for otosclerosis. The following conclusions were reached:

1. Further clinical evidence was obtained supporting the existence of the entity "pure labyrinthine otosclerosis." However, there can be difficulties in the diagnosis of this condition.

2. The incidence of vestibular symptoms in patients with otosclerosis increased as the relative and absolute amounts of sensorineural hearing loss increased and was much higher than one would expect in the normal population. In addition, with increasing sensorineural hearing loss, the severity of vestibular symptoms increased along with the incidence of depression in vestibular function determined by the bithermal caloric test in patients with vestibular symptoms.

3. A preliminary study on the administration of a combination of calcium gluconate, sodium fluoride, and vitamin D to patients with otosclerosis who had vestibular symptoms indicated that the therapy controlled vestibular symptoms in a high percentage of these patients.

4. A preliminary study on the administration of calcium gluconate, sodium fluoride, and vitamin D to patients with otosclerosis indicated that in a high percentage of patients the deterioration in hearing was stopped. A small but significant number of patients had reversal of their hearing loss.

5. Side effects of treatment with a combination of calcium gluconate, sodium fluoride, and vitamin D were not serious and were reversible, and there appears to be no contraindication to this therapy for healthy adults.

It is relatively well accepted that otosclerosis can cause sensorineural hearing loss in addition to conductive hearing loss as a result of stapes fixation. The inner ear component of the hearing loss has been called "labyrinthine or cochlear otosclerosis." In 1926, Shambaugh and Holderman[1] stated that otosclerosis could cause pure sensorineural hearing impairment without stapes fixation. The existence of pure labyrinthine otosclerosis is still a controversial subject.

Clinical and histologic evidence has been presented by Rüedi,[2] Derlacki and Valvassori,[3] Shambaugh,[4] Linthicum,[5] and Cole and Funkhouser[6] supporting the existence of the entity pure labyrinthine otosclerosis. Criteria were established by Shambaugh[4] to aid in the diagnosis of this condition. He stated that pure labyrinthine otosclerosis should be suspected in patients with bilateral sensorineural hearing loss when there is 1) a positive Schwartze sign in one or both ears, 2) a family history of stapedial otosclerosis, 3) a symmetric sensorineural loss in both ears, one of which has a fixed stapes, 4) a sensorineural loss that has unusual audiometric configurations, such as a flat, rising, or "bite-type" curve, with the greatest loss in the middle frequencies, or unusually good speech discrimination for a pure sensori-

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neural loss, or 5) a sensorineural loss that begins insidiously in early or middle adult life and progresses with no known cause. These are helpful aids in diagnosis, but compound motion tomography (polytomography or trispiral tomography) has made it possible to demonstrate replacement of the otic capsule by otosclerotic bone.[3]

The diagnosis of otosclerosis, when the hearing loss is primarily sensorineural or completely sensorineural, is of practical importance since the introduction of medical therapy for this disease by Shambaugh and Scott[7] and the subsequent reports of its effectiveness by Linthicum and associates[8] and Shambaugh and associates.[9]

On the other side of the controversy, on the basis of a temporal bone histologic study, Schuknecht and Kirchner[10] concluded that pure labyrinthine otosclerosis does not exist or at least that no convincing scientific evidence has been presented to support its existence.

Most of the voluminous literature on otosclerosis concerns hearing impairment. Although some[6,11-17] have described vestibular symptoms associated with or caused by otosclerosis, there has been no detailed analysis of vestibular symptoms experienced by patients with this disease.

The purposes of our study were to analyze a series of patients who had otosclerosis in an attempt to determine 1) whether pure labyrinthine otosclerosis exists, 2) the incidence of vestibular symptoms experienced by patients with otosclerosis, 3) if a relationship exists between vestibular symptoms and the relative and absolute amount of sensorineural hearing impairment, and 4) the effect of a combination of sodium fluoride, calcium gluconate, and vitamin D on vestibular symptoms and hearing loss caused by otosclerosis.

METHODS AND MATERIALS

A consecutive series of patients with otosclerosis seen between mid-1973 and December 31, 1976 were selected for the study. This period was chosen because, during this time, we began evaluating patients suspected of having otosclerosis with multiple 1-mm thick trispiral tomograms of the petrous bones and treating otosclerotic patients with sodium fluoride, calcium gluconate, and vitamin D. Patients treated with this medical regimen received 500 mg of calcium gluconate before breakfast and before dinner at night, and 20 mg of sodium fluoride, either in capsule or enteric-coated tablet form, after these two meals. The patient was instructed to separate the ingestion of the drugs not only by a meal but also by at least an hour in time. The patients also took one multivitamin tablet with 400 units of vitamin D daily.

In trispiral tomographic studies of the ear, we use primarily the semiaxial projection as described by Rovsing,[18] and usually 12 1-mm sections or cuts are obtained. Only in unusual situations is the pyramidal projection used.[18]

All patients had determinations of pure tone air and bone conduction thresholds, speech reception thresholds, and speech discrimination scores. In addition, many patients had tone decay testing and impedance audiometry studies. In categorizing and evaluating auditory acuity, the air and bone conduction thresholds for the five tones, 250, 500, 1,000, 2,000, and 4,000 Hz, were averaged.

Many patients had bithermal caloric testing. Nystagmus evoked by the caloric test was recorded by electronystagmography. A difference in the response of each labyrinth of 20% or more was considered significant.

PATIENTS IN STUDY

Between mid-1973 and December 31, 1976, 849 patients with otosclerosis were seen in the Otolaryngology Department of the Mayo Clinic. Thirty-five patients were excluded from the study because the mean pure tone air conduction thresholds for the five frequencies were 20 dB or better (normal hearing range). One hundred and eight patients were excluded because they had had bilateral operations for otosclerosis (stapedectomy, stapes mobilization, fenestration of the horizontal semicircular canal), unilateral operations for otosclerosis and normal hearing in the other ear, and unilateral operations for otosclerosis and hearing loss in the unoperated ear but had received no medical therapy for otosclerosis. Eight patients were excluded because, in addition to otosclerosis, they had another ear disease, such as serous otitis media or chronic suppurative otitis media.

In order to evaluate adequately changes in the otic capsule that are consistent with otosclerosis, unless the disease is extremely extensive, 1-mm cut compound motion tomograms are necessary. One hundred and twenty patients with a minimal conductive component to the hearing loss or a pure sensorineural loss were excluded because cuts of only 2 or 3 mm were obtained or the 1-mm cut showed changes in the otic capsule that were suggestive, but not diagnostic, of otosclerosis. In addition, 32 patients with sensorineural hearing loss were excluded because, although otosclerosis was diagnosed on the basis of the 1-mm cut trispiral tomograms, a subsequent review of the tomograms did not reveal any roentgenographic abnormalities. This emphasizes one of the difficulties in diagnosing labyrinthine otosclerosis on the basis of roentgenographic studies. There are patients who have extensive changes in the otic capsule that are clearly consistent with otosclerosis (cases included in this study), patients who have no abnormalities in the otic capsule (normal), and patients who have gradations of roentgenographic changes between these extremes. When the changes are minimal, it is difficult to be certain of the diagnosis. Five hundred and forty-six patients were left in the actual analysis. Of these 546 patients, 500 had not had previous ear surgery and were placed into four groups according to the relative proportion of their hearing loss that was sensorineural. The remaining 46 patients had prior unilateral stapedectomy for otosclerosis and a hearing loss diagnosed as being caused by otosclerosis in the unoperated ear and received medical therapy for otosclerosis.

Group I. Patients in group I had hearing losses in which 50% or more of the loss was conductive. Many of these patients had minimal or no sensorineural hearing loss. Most patients were candidates for stapedectomy, and several of them subsequently had an exploratory tympanotomy, and the diagnosis of otosclerosis was confirmed. The mean bone conduction threshold for the five frequencies for the hearing-impaired ears of the 57 patients in this group was 21 dB.

Group II. Patients of group II had hearing losses in which 51% or more of the loss was sensorineural, with a minimum mean conductive loss of 10 dB for the five frequencies. Several of these patients had a substantial conductive component to the hearing impairment and were candidates for stapedectomy, and a few subsequently had an exploratory tympanotomy and the diagnosis of otosclerosis was confirmed. The mean bone conduction threshold for the hearing-impaired ears of the 117 patients in this group was 40 dB.

Group III. Patients in group III primarily had a sensorineural hearing loss but also had a slight mean conductive loss of 2 to 9 dB for the five frequencies. The mean bone conduction threshold for the hearing-impaired ears of the 181 patients in this group was 44 dB.

Group IV. Patients in group IV had a pure sensorineural hearing loss. The mean bone conduction threshold for the hearing-impaired ears of the 145 patients in this group was 49 dB.

Group V. Patients of group V had a prior unilateral stapedectomy for otosclerosis and a hearing loss in the unoperated ear diagnosed as being caused by otosclerosis, and received medical therapy for otosclerosis. The mean bone conduction threshold for the unoperated ears of the 46 patients in this group was 32 dB. Categorization of the 46 patients by type of hearing impairment in the unoperated ear placed 16 of the patients in group I, 21 in group II, 2 in group III, and 7 in group IV. Because of the prior ear surgery, group V could not be used in the analysis of vestibular symptoms. However, the unoperated ear could be used in the analysis of the effects of medical therapy on hearing loss.

Sex Distribution. Group I was composed of 37 (65%) females and 20 (35%) males; group II, 73 (62%) females and 44 (38%) males; group III, 88 (49%) females and 93 (51%) males; group IV, 81 (56%) females and 64 (44%) males; and group V, 32 (70%) females and 14 (30%) males. Thus, in all but group III, females predominated. In group III, the sex incidence was almost equal.

Family History of Hearing Loss. In group I, 32 (56%) of the patients had family histories of hearing loss, and 16 of these patients had histories of otosclerosis (28% of the total group). Twenty-three (40%) of the patients did not have family histories of hearing impairment. In group II, 59 (51%) of the patients had family histories of hearing loss, and 7 of the patients had histories of otosclerosis (6% of the total group). Fifty-eight (50%) patients did not have family histories of hearing impairment. In group III, 105 (58%) of the patients had family histories of hearing loss and 16 had histories of otosclerosis (9% of the total group). Seventy-six patients (42%) did not have family histories of hearing impairment. In group IV, 79 (54%) of the patients had family histories of hearing loss, and 16 of the patients had histories of otosclerosis (11% of the total group). Sixty-six (46%) of the patients did not have histories of hearing impairment. In group V, 24 (52%) of the patients had family histories of hearing loss, and 5 of the patients had histories of otosclerosis (11% of the total group). Twenty-two (48%) of the patients did not have family histories of hearing impairment. Therefore, most of the patients in each group had family histories of hearing loss, and a significant number of patients also had histories of otosclerosis.

Incidence of Bilateral Hearing Loss. In group I, 29 (51%) of the patients had bilateral hearing loss and 28 (49%) unilateral hearing loss (total of 86 ears). In group II, 93 (79%) of the patients had bilateral hearing loss and 24 (21%) unilateral loss (total of 210 ears). In group III, 131 (72%) of the patients had bilateral hearing loss and 50 (28%) unilateral hearing loss (total of 312 ears). In group IV, 106 (73%) of the patients had bilateral hearing loss and 9 (27%) unilateral hearing loss (total of 251 ears). The patients in group V were selected for the study because they had bilateral hearing loss and had undergone unilateral stapedectomy. Because only the unoperated ear could be included, a total of 46 ears with hearing impairment could be analyzed. Therefore, among the five groups, most patients had bilateral hearing loss, and the 546 patients had a total of 905 ears with hearing impairment.

Incidence of Fluctuant Hearing Loss. Almost all of the 905 ears had audiometric documentation of a progressive loss of hearing. A few had hearing impairment develop suddenly. In each group there was a history or audiometric documentation of ears having fluctuation in auditory acuity. However, in most of these ears the hearing loss tended to be progressive as well. In group I, 3 (3%) of the ears had fluctuation in auditory acuity; in group II, 14 (7%) of the ears; in group III, 48 (15%); in group IV, 44 (18%); and in group V, 1 (2%) of the unoperated ears. Thus, although some ears in each group had histories of fluctuation in auditory acuity, the incidence tended to be higher as the relative and absolute amounts of the hearing impairment became sensorineural.

Comment. The five groups were similar in that most patients in each group had bilateral hearing loss and family histories of hearing impairment, with a significant number of patients also having histories of otosclerosis. With the exception of group III, in which the sex incidence was almost equal, females predominated. In each group, some ears had fluctuant hearing loss, the incidence being higher as the sensorineural hearing loss increased.

PURE LABYRINTHINE OTOSCLEROSIS

Pure labyrinthine otosclerosis not only exists but it also is a common cause of sensorineural hearing loss. This opinion is based on four observations: 1) the existence in certain patients of bilateral progressive sensorineural hearing loss of equal magnitude with a conductive hearing loss in one ear due to stapes fixation and similar roentgenographic changes consistent with otosclerosis in the otic capsule bilaterally, 2) the existence in certain patients of progressive sensorineural hearing loss with roentgenographic changes in the otic capsule consistent with otosclerosis and the later development of a superimposed conductive hearing loss, 3) the reversal

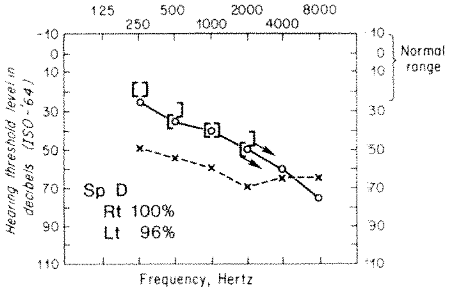

Fig. 1. (Case 1) Audiogram of 58-year-old male. Sp D - Speech discrimination.

of roentgenographic changes consistent with otosclerosis in the otic capsule by medical therapy in patients with sensorineural hearing loss, and 4) in certain patients with roentgenographic changes consistent with otosclerosis in the otic capsule, the reversal of progressive sensorineural hearing loss by medical therapy. These observations can be illustrated by brief case reports.

Case 1. A 58-year-old male had experienced bilateral progressive hearing loss for 15 years. He had a family history of hearing impairment. An audiogram (Fig. 1) showed a bilateral symmetric sensorineural hearing loss. In addition, there was a significant conductive hearing loss in the left ear. Trispiral tomograms of the petrous bones (Fig. 2) revealed changes in the otic capsule along the basal coils of the cochleae, consistent with otosclerosis. They were slightly more marked on the left than the right. Similar changes were evident in the oval window area on the left but not on the right. (For comparison, the findings in a normal patient are illustrated in Figure 3.) Otosclerosis on the left was confirmed by exploratory tympanotomy and stapedectomy that resulted in closure of the air-bone gap. It seems unreasonable to assume that the otosclerotic process was causing a progressive sensorineural hearing loss in the left ear, because stapes fixation could be demonstrated, whereas a similar sensorineural hearing loss on the right with similar roentgenographic changes in the otic capsule — with the exception of the oval window area — is due to some other disease process.

Case 2. A 42-year-old male was seen on May 31, 1966, with an 11-year history of a progressive hearing loss in his right ear and the recent onset of hearing loss in his left ear. He had a family history of hearing impairment. An audiogram (Fig. 4) showed a moderately severe sensorineural hearing loss on the right and a mild high-tone sensorineural hearing loss on the left. The cause of the hearing loss at this time was not identified. The patient was next seen on February 18, 1975, because of rapidly deteriorating hearing in both ears. In addition, he had been having frequent recurrent attacks of objective rotatory vertigo with nausea and vomiting and had chronic postural unsteadiness. An audiogram (Fig. 5) now showed an extremely severe sensorineural hearing loss on the right and a moderately severe sensorineural hearing loss on the left. However, there was now a mild conductive component to the hearing loss on the left. Trispiral tomograms (1-mm cuts) of the petrous bones on February 19, 1975 (Fig. 6), revealed extensive changes in both otic

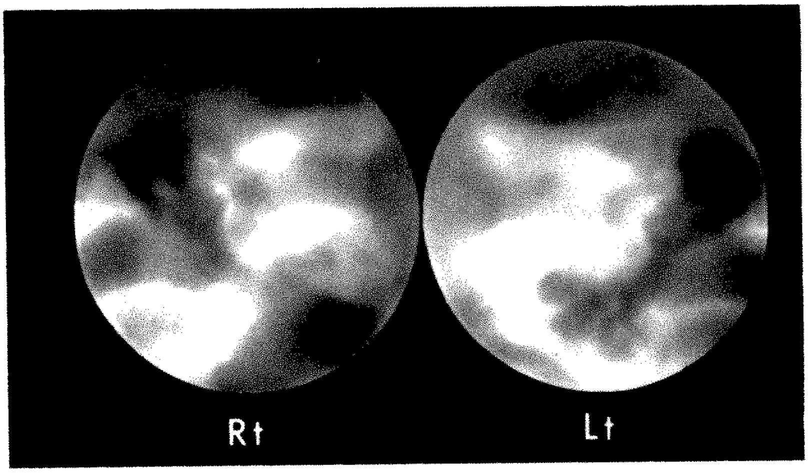

Fig. 2. (Case 1) Trispiral tomograms of the ears of 58-year-old male showing asymmetric involvement. There is virtual obliteration of the oval window on the left from marginal blunting encroachment and stapedial footplate thickening. The oval window is open on the right. The basal coil of the cochlea exhibits irregularly thickened and demineralized bony walls which compromise the lumen, most markedly on the left.

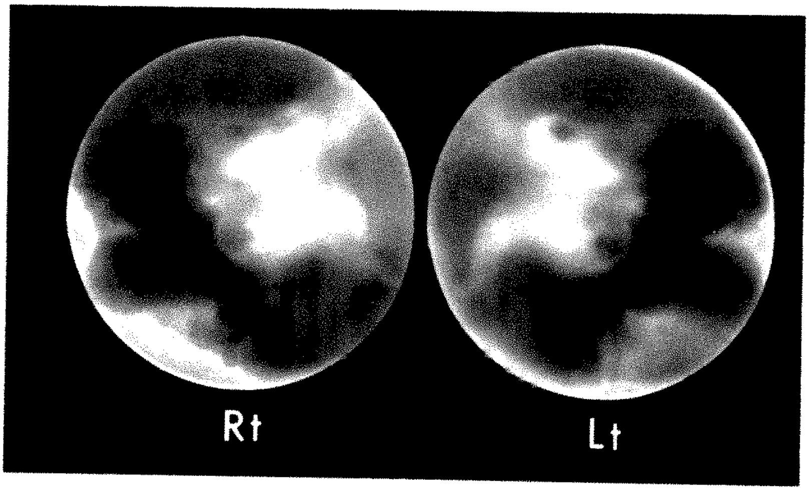

Fig. 3. Normal trispiral tomograms of the ear from a patient not described for comparison with the abnormal. Note the widely patent oval windows, the thin, dense bony capsule of the basal turns, and the widely patent cochlear lumens. The stapedial footplate is invisible or only marginally visible.

capsules consistent with otosclerosis. Therapy with calcium gluconate, sodium fluoride, and vitamin D stabilized the hearing (Fig. 5) and stopped the dizziness. After two years of therapy, there was dramatic remineralization of the basal coil of the cochlea on the left (Fig. 6B) and slight remineralization on the right (Fig. 6A). The response of the symptoms to medical therapy and in particular the dramatic remineralization of the otic capsule on the left would seem to confirm the diagnosis of labyrinthine otosclerosis. Such a diagnosis probably could have been made before 1975 even though evidence of stapes fixation was lacking. However, we agree with Linthicum and associates[8] that evaluating the changes in otosclerotic foci in the otic capsule is very difficult with compound motion tomography after medical therapy unless the changes are unusually dramatic, such as demonstrated in the left ear of this patient.

Case 3. A 48-year-old male was seen on January 28, 1975, with a history of a progressive hearing loss in the left ear. An audiogram (Fig. 7) showed a mild mixed hearing loss on the left. Trispiral tomograms (1-mm cuts) of the petrous bones revealed changes in each otic capsule, consistent with otosclerosis, but more marked on the left. In addition, there was a negative stapedius reflex on the left. Therapy with calcium gluconate, sodium fluoride, and vitamin D gradually reversed the hearing loss in the left ear. Two years of therapy resulted in complete reversal of both the conductive and sensorineural components of the hearing loss in the left ear for the tones between 250 and 2,000 Hz (Fig. 7). This case demonstrates clearly that medical therapy occasionally can reverse both a conductive and a sensorineural hearing loss due to otosclerosis.

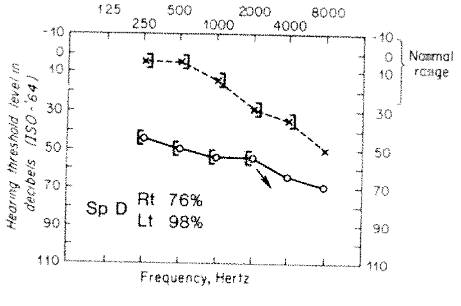

Fig. 4. (Case 2) Audiogram of 42-year-old male made on May 31, 1966. Sp D – Speech discrimination.

Case 4. A 43-year-old male was seen on July 20, 1973, with a history of a progressive hearing loss that mainly involved the left ear and developed over the previous five years. He had a family history of otosclerosis. An audiogram (Fig. 8) revealed a mild to moderately severe sensorineural hearing loss on the left and a mild high-tone sensorineural hearing loss on the right. Trispiral tomograms of the petrous bones revealed changes in the otic capsules consistent with otosclerosis. The patient was given a combination of sodium fluoride, calcium gluconate, and vitamin D, and a gradual reversal of a significant amount of the sensorineural hearing loss in the left ear occurred between the 4th and the 12th month of therapy. This reversal in hearing loss has been maintained over a 31-month period (Fig. 8). Several years ago, we would have attributed the progressive sensorineural hearing loss to presenile presbycusis. In our experience, this type of hearing loss does not spontaneously reverse. The diagnosis of labyrin-

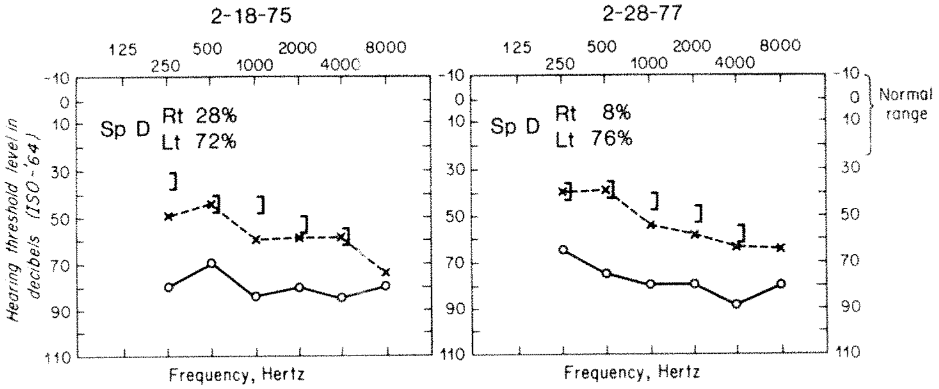

Fig. 5. (Case 2) Audiograms of 42-year-old male made on Feb. 18, 1975, and February 28, 1977. Sp D - Speech discrimination.

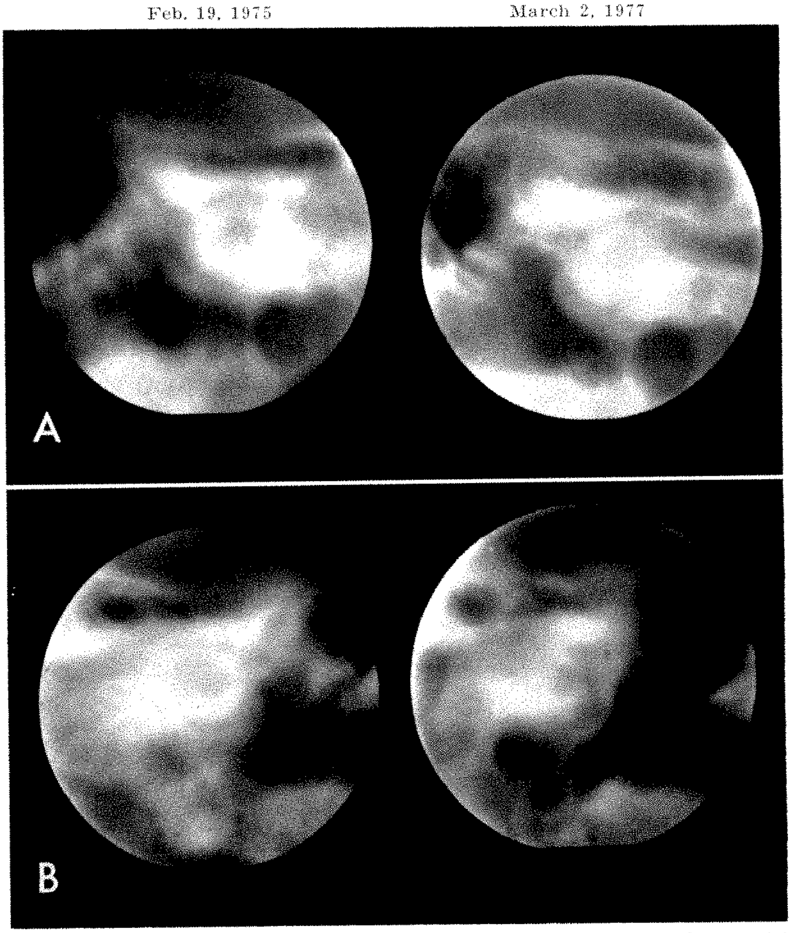

Fig. 6. (Case 2) Trispiral tomograms of 42-year-old male. A) Right ear. Marked demineralization and irregular thickening of basal coil of the cochlea, with narrowing of its lumen and poor delineation of the oval window on February 19, 1975. Two years later, March 2, 1977, remineralization is apparent so that the oval window and cochlear lumen are more easily seen. B) Left ear, on Feb. 19, 1975, irregular thickening and demineralization of the basal coil of the cochlea is apparent and the lumen is poorly delineated. By March 2, 1977, these changes have disappeared, and except for minimal widening of the bony capsule of the basal turn, the examination results are normal.

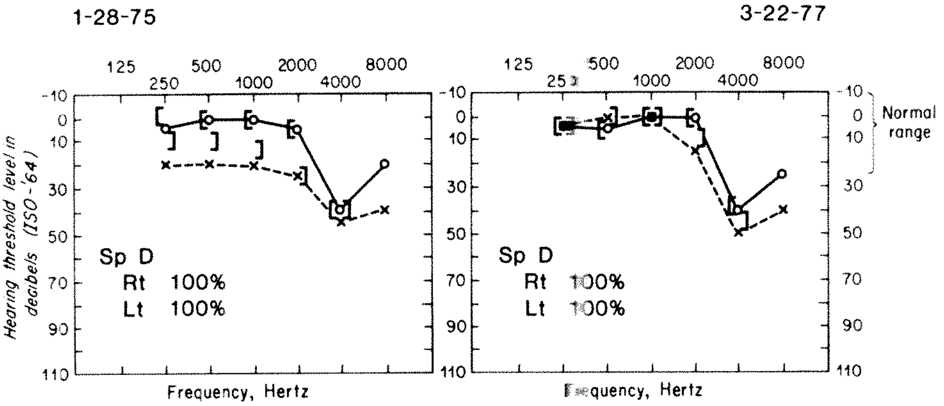

Fig. 7. (Case 3) Audiograms of 48-year-old male made on Jan. 28, 1975, and March 22, 1977. Sp D - Speech discrimination.

thine otosclerosis would seem to be confirmed by the response to medical therapy.

Case 5. A 27-year-old male was seen on March 18, 1976, with a history of a rapidly progressing hearing loss on the right after being hit on the right side of the head with a softball one year before. For six months, there had been a rapidly progressive hearing loss on the left. The progressive nature of the hearing impairment in both ears had been documented by serial audiograms. He also had experienced several spontaneous attacks of objective rotatory vertigo with nausea and vomiting. There was no family history of hearing impairment. Thorough otolaryngologic, neurologic, and general examinations did not reveal the cause of the hearing impairment. However, trispiral tomograms of the petrous bones revealed changes in both otic capsules, consistent with otosclerosis. An audiogram (Fig. 9) showed almost a complete sensorineural hearing loss on the right and a severe sensorineural hearing loss on the left. In addition, there appeared to be a conductive component to the hearing loss on the left at 250 and 500 Hz. The patient was given a combination of sodium fluoride, calcium gluconate, and vitamin D and experienced progressive and dramatic recovery of hearing in his left ear and significant improvement in hearing in his right ear beginning after 2½ months of therapy and continuing through 17 months of therapy (Fig. 9). The vertigo stopped completely. A small conductive element to the hearing loss was noted for the low tones in the left ear, suggestive of some fixation of the stapes in that ear. This was not a sudden hearing loss in either ear, and a rapidly progressive sensorineural hearing loss occurring over several months would not be expected to reverse spontaneously. The diagnosis of labyrinthine otosclerosis would seem to be confirmed by the response to medical therapy.

Case 6. A 60-year-old male had a bilateral progressive hearing loss for 31 years. The loss had resulted in an almost complete sensorineural hearing impairment (Fig. 10) when he was first seen on June 4, 1976. At no time had

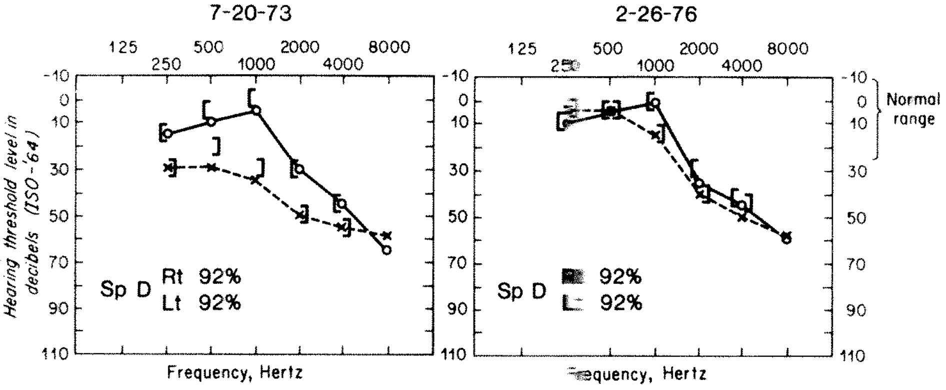

Fig. 8. (Case 4) Audiograms of 43-year-old male made on July 20, 1973, and Feb. 26, 1976. Sp D - Speech discrimination.

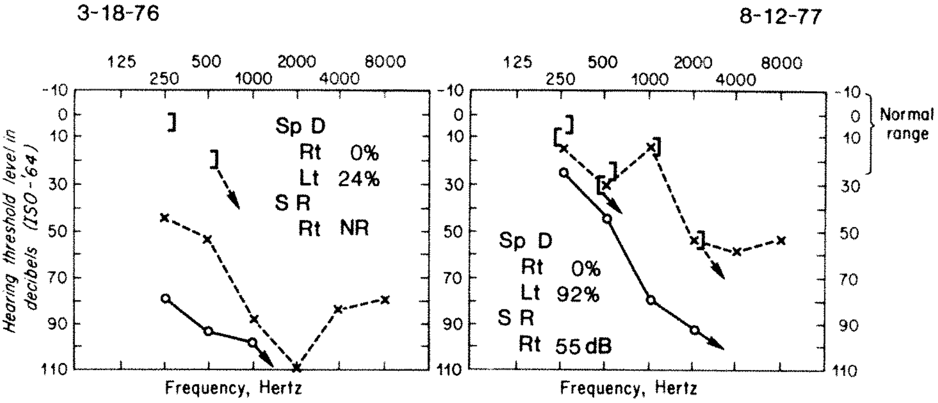

Fig. 9. (Case 5) Audiograms of 27-year-old male made on March 18, 1976, and Aug. 12, 1977. Sp D - Speech discrimination; S R - Speech reception.

a conductive component to the hearing loss been demonstrated. Trispiral tomograms of the petrous bones revealed changes in both otic capsules, consistent with otosclerosis. He was given a combination of sodium fluoride, calcium gluconate, and vitamin D and, between the 5th and the 12th month of therapy, experienced a substantial progressive reversal of the sensorineural hearing loss (Fig. 10). A progressive sensorineural hearing loss of this type would not be expected to spontaneously reverse. The diagnosis of labyrinthine otosclerosis would seem to be confirmed by the response to medical therapy.

Comment. Although these case reports offer further clinical evidence in support of the existence of the entity pure labyrinthine otosclerosis, the most compelling evidence was the reversal of sensorineural hearing loss by medical therapy when spontaneous reversal of the hearing impairment could not be expected; however, conclusive evidence must await further histologic studies.

VESTIBULAR SYMPTOMS

In the analysis of the vestibular symptoms of patients with otosclerosis, patients with previous ear surgery were excluded. Thus, only the patients in groups I through IV were used in this portion of the study.

Types of Vestibular Symptoms. Vestibular symptoms experienced by patients in groups I through IV could be classified under three categories: spontaneous recurrent attacks, a spontaneous single episode, and postural.

The spontaneous recurrent attacks of vestibular symptoms were described by

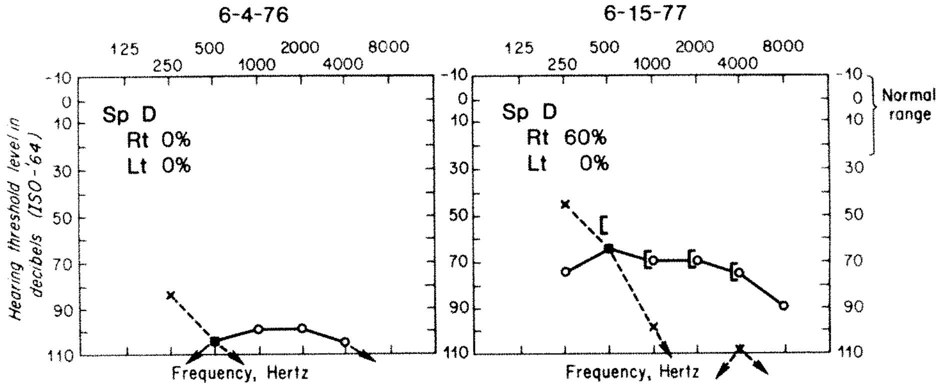

Fig. 10. (Case 6) Audiograms of 60-year-old male made on June 4, 1976, and June 15, 1977. Sp D - Speech discrimination.

TABLE 1. INCIDENCE OF VESTIBULAR SYMPTOMS IN 500 PATIENTS WITH OTOSCLEROSIS

		Vertigo						*Imbalance*					
		Recurrent Attacks		*Postural*		*Single Episode*		*Recurrent Attacks*		*Postural*		*Single Episode*	
Group	*No. of Patients*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
I	57	3	5	5	9	2	4	0	0	10	18	0	0
II	117	26	22	11	9	1	1	1	1	22	19	0	0
III	181	52	29	18	10	4	2	7	4	41	23	0	0
IV	145	51	35	23	16	3	2	4	3	37	26	1	1

the patients as either true vertigo or severe imbalance without a hallucination of motion. Vertigo usually consisted of an objective hallucination of motion and only rarely a subjective hallucination of motion. The attacks of vertigo were typical of the vertiginous episodes associated with idiopathic endolymphatic hydrops (Ménière's disease). The recurrent attacks of vertigo or imbalance usually were associated with nausea and vomiting and rarely, diarrhea. Typically, the attacks lasted one to two hours, but they varied in length from minutes to 72 hours. The frequency of the attacks varied from daily to once a year.

A spontaneous single episode of vestibular symptoms was described by the patients as either true vertigo or severe imbalance without a hallucination of motion. The episodes of vertigo or imbalance were usually associated with nausea and vomiting. The single episodes lasted anywhere from a few hours to three weeks. However, most of the episodes were protracted and typical of vestibular symptoms resulting from sudden depression in the vestibular function of one or both labyrinths.

Postural vestibular symptoms were described by the patients as either objective vertigo or imbalance without a hallucination of motion. The severity of the postural vestibular symptoms varied from mild to severe, and the frequency varied from rare to chronic. Occasionally, postural vestibular symptoms were associated with nausea. Only rarely was postural vertigo associated with vomiting. The postural vestibular symptoms lasted from a few seconds to a minute and were precipitated by changes in the position of the head or rapid movements of the body.

Incidence of Vestibular Symptoms. In group I, 15 (26%) of the patients experienced vestibular symptoms and 42 (74%) of the patients did not. In group II, 46 (39%) of the patients experienced vestibular symptoms and 71 (61%) did not. In group III, 86 (48%) of the patients experienced vestibular symptoms and 95 (52%) did not. In group IV, 83 (57%) of the patients experienced vestibular symptoms and 62 (43%) of the patients did not. Thus, the incidence of vestibular symptoms increased as the relative and absolute amounts of sensorineural hearing loss increased.

Six different types of vestibular symptoms were experienced by the patients (Table 1). Some patients experienced more than one type of vestibular symptom.

Recurrent spontaneous attacks of vertigo were the most severe vestibular symptom. Thus, not only did the incidence of vestibular symptoms increase with the amount of sensorineural hearing loss but also the degree of severity of vestibular symptoms.

Recurrent spontaneous attacks of imbalance were uncommon, but once again the incidence increased as the amount of sensorineural hearing loss increased, this symptom being primarily experienced by patients in groups III and IV (Table 1).

In patients with otosclerosis, postural imbalance was almost twice as frequent as postural vertigo (Table 1). Although the incidence of both postural vertigo and postural imbalance increased with the degree of sensorineural hearing loss, the increase was more modest than that seen with recurrent spontaneous attacks of vestibular symptoms. However, the severity and frequency of postural vestibular symptoms tended to increase as the amount of sensorineural hearing loss increased.

A single spontaneous episode of vertigo was not common, and the relative incidence was similar in the four groups (Table 1). There was only one single spontaneous episode of imbalance and this occurred in group IV (Table 1).

In an analysis of patients with otosclerosis that corresponded to the patients in group I, Cawthorne[11] stated, "A history of vertigo, usually slight and momentary when stooping, was given in 24% of the cases." The findings in the patients in group I were almost identical. Twenty-six percent of the patients in group I experienced vestibular symptoms. There was a patient episode incidence of postural vestibular symptoms (vertigo and imbalance together) of 26.5% and a patient episode incidence of recurrent spontaneous attacks of vestibular symptoms in only 5%.

The incidence and severity of vestibular symptoms experienced by patients with otosclerosis increase as the relative and absolute amounts of sensorineural hearing loss increase. And, we would agree with Cawthorne[11] that the incidence of vestibular symptoms in patients with otosclerosis is far higher than one would expect in the normal population. This holds true even if one chooses to ignore group IV (composed of patients with pure labyrinthine otosclerosis). In addition, the correlation between inner ear hearing impairment and the incidence and severity of vestibular symptoms indicates that the vestibular symptoms are due to the otosclerotic process.

Bithermal Caloric Test. The bithermal caloric test was performed on 13 (87%) of the 15 patients with vestibular symptoms in group I, 38 (83%) of the 46 patients with vestibular symptoms in group II, 71 (83%) of the 86 patients with vestibular symptoms in group III, and 70 (84%) of the 83 patients with vestibular symptoms in group IV. When abnormal vestibular function was demonstrated, it usually consisted of unilateral depression in labyrinthine function, occasionally bilateral depression in function, and rarely unilateral absence of function. In group I, of the 13 patients who had the bithermal caloric test, the results were normal in 9 (69%) and abnormal in 4 (31%). In group II, of the 38 patients who were tested, the results were normal in 18 (47%) and abnormal in 20 (53%). In group III, of the 71 patients who were tested, the results were normal in 27 (38%) and abnormal in 44 (62%). In group IV, of the 70 patients who were tested, the results were normal in 24 (34%) and abnormal in 46 (66%). Thus, not only did the incidence and severity of vestibular symptoms increase in patients with otosclerosis as the relative and absolute amounts of sensorineural hearing loss increased, but in those patients with vestibular symptoms, the incidence of demonstrable depression in labyrinthine function also increased.

Patients in the Analysis of the Results of Therapy for Vestibular Symptoms. Most of the patients in this study with otosclerosis and vestibular symptoms were treated with the Shambaugh et al[9] medical regimen consisting of calcium gluconate, sodium fluoride, and vitamin D. The ten occurrences of a single spontaneous episode of vertigo and the one occurrence of a single spontaneous episode of imbalance (Table 1) were not included in the evaluation of the results of therapy.

In group I, of the 15 patients with vestibular symptoms, 10 (66.7%) were treated and followed up, 1 (6.7%) had ear surgery at the beginning of therapy and thus had to be excluded from the analysis, 1 (6.7%) was not due for the first posttherapy evaluation at the time of this analysis, and 3 (20%) were lost to follow-up. In group II, of the 46 patients with vestibular symptoms, 28 (61%) were treated and followed up, 2 (4%) had ear surgery at the beginning of therapy and thus had to be excluded from the analysis, 4 (9%) were not due

TABLE 2. RESULTS OF THERAPY FOR RECURRENT SPONTANEOUS ATTACKS OF VERTIGO IN PATIENTS WITH OTOSCLEROSIS

		Control of Vertigo							
		Success						*Failure*	
		100%		*50-99%*		*Total*		*0-49%*	
Group	*No. of Patients*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
I	2	1	50	1	50	2	100	0	0
II	21	15	71	4	19	19	90	2	10
III	35	28	80	4	11	32	91	3	9
IV	28	17	61	8	28	25	89	3	11

for the first posttherapy evaluation at the time of this analysis, and 12 (26%) have been lost to follow-up. In group III, of the 86 patients with vestibular symptoms, 50 (58%) were treated and followed up, 5 (6%) received no treatment, and 10 (12%) had ear surgery at the beginning of therapy and thus had to be excluded from the analysis, 8 (9%) were not due for the first posttherapy evaluation at the time of this analysis, and 13 (15%) have been lost to follow-up. In group IV, of the 83 patients with vestibular symptoms, 44 (53%) were treated and followed up, 1 (1%) received no treatment, 5 (6%) had ear surgery at the beginning of therapy and thus had to be excluded from the analysis, 8 (10%) were not due for the first posttherapy evaluation at the time of this analysis, and 25 (30%) have been lost to follow-up.

The mean and range in duration of therapy for patients with vestibular symptoms who were treated and followed up in group I was 15 months (6 to 25 months), in group II 15 months (6 to 44 months), in group III 16 months (6 to 36 months), and in group IV 14 months (6 to 36 months). Although the duration of therapy was similar for the four groups, the mean duration of therapy was relatively short, and thus this can be considered a preliminary report on the effects of therapy on vestibular symptoms.

Results of Therapy on Recurrent Attacks of Vertigo. Satisfactory or successful treatment was judged to have occurred if control of vertigo was at least 50%. If control of vertigo was less than 50%, therapy failed.

In group I, there were only two patients who had recurrent attacks of vertigo and were treated and followed up. One patient was completely relieved of vertigo and the other markedly improved (Table 2). Satisfactory control of vertiginous attacks occurred in 90% of the patients in group II, 91% in group III, and 89% in group IV. One patient in group IV who had complete control of recurrent spontaneous attacks of vertigo developed mild postural imbalance which he had not experienced before treatment. Therefore, a high percentage of patients and a similar percentage of patients in the four groups had satisfactory control of recurrent spontaneous attacks of vertigo while on medical therapy. In addition, a significant number of patients had complete control of vertigo (Table 2). In some of these patients, the attacks were frequent and severe and had not been influenced by the usual medical therapies for idiopathic endolymphatic hydrops, and yet complete control was achieved with therapy for otosclerosis. Successful control of the vertiginous attacks was usually achieved during the first 3 to 12 months of therapy. Frequently the frequency and severity of the attacks diminished gradually. If the attacks of vertigo were not controlled during the first year of therapy, they usually were not during the second.

Results of Therapy on Recurrent Attacks of Imbalance. No patient in group I and only one in group II experienced recurrent spontaneous attacks of imbalance. This patient was completely relieved with medical therapy. In group III, of the four patients who experienced recurrent attacks of imbalance

TABLE 3. RESULTS OF THERAPY FOR POSTURAL VERTIGO IN PATIENTS WITH OTOSCLEROSIS

		Control of Vertigo							
		Success							
		100%		*50-99%*		*Total*		*Failure 0-49%*	
Group	*No. of Patients*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
I	3	3	100	0	0	3	100	0	0
II	5	4	80	1	20	5	100	0	0
III	11	6	55	2	18	8	73	3	27
IV	10	5	50	2	20	7	70	3	30

and were treated and followed up, three (75%) were completely relieved; in the other patient, therapy was of no benefit. In group IV, of the two patients who experienced recurrent attacks of imbalance and were treated and followed up, one (50%) was completely relieved and the other (50%) received no benefit. Although only seven patients experienced recurrent spontaneous attacks of imbalance and were treated and followed up, the response to therapy was similar to that of patients with recurrent attacks of vertigo.

If the patient episodes of recurrent spontaneous attacks of vertigo and imbalance are lumped together, then 100% of these episodes were satisfactorily controlled in group I, 91% in group II, 90% in group III, and 87% in group IV. These impressive statistics suggest that calcium gluconate, sodium fluoride, and vitamin D have a beneficial effect in controlling recurrent spontaneous attacks of vestibular symptoms experienced by patients with otosclerosis and thus in controlling the disease process.

Results of Therapy on Postural Vertigo. In group I, only three patients experienced postural vertigo and were treated and followed up (Table 3). All three had complete control of the vertigo. Satisfactory control of postural vertigo occurred in all patients in group II, 73% of the patients in group III, and 70% of the patients in group IV. Therefore, a high percentage of patients in the four groups had satisfactory control of postural vertigo. Although several patients had mild and infrequent postural vertigo and very likely could have had spontaneous resolution of the symptom, there were patients, particularly in groups III and IV, who had had severe, almost constant postural vertigo for a number of years and who had dramatic improvement on therapy. Response to therapy of postural vertigo was similar to that of recurrent spontaneous attacks of vestibular symptoms, successful control of postural vertigo usually being achieved during the first 3 to 12 months of therapy.

Results of Therapy on Postural Imbalance. Satisfactory control of postural imbalance occurred in 57% of the patients in group I, all of the patients in group II, 50% in group III, and 57% in group IV (Table 4). Therefore, with the exception of group II in which all patients had satisfactory control of postural imbalance, the results of therapy were

TABLE 4. RESULTS OF THERAPY FOR POSTURAL IMBALANCE IN PATIENTS WITH OTOSCLEROSIS

		Control of Imbalance							
		Success							
		100%		*50-99%*		*Total*		*Failure 0-49%*	
Group	*No. of Patients*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
I	7	3	43	1	14	4	57	3	43
II	11	9	82	2	18	11	100	0	0
III	18	5	28	4	22	9	50	9	50
IV	21	8	38	4	19	12	57	9	43

TABLE 5. PATIENTS WITH OTOSCLEROSIS AND HEARING LOSS

Group	Patients Total	Patients Followed up	No. of Ears	Follow-up (mo) Mean	Follow-up (mo) Range
I	57	34	51	16.0	4-29
II	117	64	109	16.5	6-44
III	181	102	167	15.0	5-36
IV	145	77	132	14.0	6-36
V	46	46	46	13.0	4-31

similar. One patient who did not have vestibular symptoms before treatment developed mild postural imbalance while being treated. As with postural vertigo, some patients with mild and infrequent postural imbalance could have had spontaneous resolution of the symptom. However, some patients, particularly in groups III and IV, had experienced severe, almost chronic postural imbalance for several years but had dramatic improvement while on therapy.

Overall, a higher percentage of patients on medical therapy achieved satisfactory control of postural vertigo (Table 3) than postural imbalance (Table 4). However, the incidence of satisfactory control of both postural vertigo and postural imbalance was impressive. This was particularly true for patients who had severe, almost chronic postural vestibular symptoms and who received no relief from other forms of medical therapy, but had dramatic improvement while receiving calcium gluconate, sodium fluoride, and vitamin D. The response of some of these patients to therapy was just as compelling a reason for the efficacy of the therapy as was the response of recurrent spontaneous attacks of vestibular symptoms. If the patient episodes of postural vertigo and postural imbalance are lumped together, then 70% of these episodes were satisfactorily controlled in group I, 100% in group II, 59% in group III, and 61% in group IV.

HEARING LOSS

Patients in the Analysis of the Results of Therapy for Hearing Loss. Most of the patients in this study with otosclerosis were treated with the Shambaugh et al[9] medical regimen of calcium gluconate, sodium fluoride, and vitamin D. In group I, of the 57 patients, 34 (60%) were treated and followed up, 1 (2%) received no treatment and was excluded from the analysis of the effect of therapy on hearing, 7 (12%) were not due for their first posttherapy evaluation at the time of this analysis, and 15 (26%) have been lost to follow-up. In group II, of the 117 patients, 64 (55%) were treated and followed up, 4 (3%) received no treatment, and 1 (1%) had ear surgery at the beginning of therapy and thus had to be excluded from the analysis, 13 (11%) were not due for their first posttherapy evaluation at the time of this analysis, and 35 (30%) have been lost to follow-up. In group III, of the 181 patients, 102 (56%) were treated and followed up, 13 (7%) received no treatment, 2 (1%) had ear surgery at the beginning of therapy and thus had to be excluded from the analysis, 16 (9%) were not due for their first posttherapy evaluation at the time of this analysis, and 48 (27%) have been lost to follow-up. In group IV, of the 145 patients, 77 (53%) were treated and followed up, 5 (4%) received no treatment, and 3 (2%) had ear surgery at the beginning of therapy and thus had to be excluded from the analysis, 16 (11%) were not due for their first posttherapy evaluation, and 44 (30%) have been lost to follow-up. The 46 patients in group V were selected because they had been treated and followed up. Thus, the percentage of patients treated and followed up and the percentage of patients lost to follow-up in groups I through IV was essentially the same. The mean duration of therapy was relatively short, and thus this can be considered as a preliminary report on the effects of therapy on hearing loss (Table 5).

TABLE 6. RESULTS OF THERAPY IN PATIENTS WITH OTOSCLEROSIS AND HEARING LOSS

		Hearing Results							
				Success					
	No. of	*No Change*		*Improved*		*Total*		*Failure (Worse)*	
Group	*Ears*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
I	51	36	70	7	14	43	84	8	16
II	109	77	71	18	16	95	87	14	13
III	167	113	68	30	18	143	86	24	14
IV	132	90	68	26	20	116	88	16	12
V	46	37	81	1	2	38	83	8	17

Results of Therapy on Hearing Loss. A significant change in hearing was considered to have occurred if there was a mean change for the five tones of 10 dB or more in air conduction thresholds with or without a 10% or greater change in speech discrimination score (conductive change), a mean change for the five tones of 10 dB or more in air conduction and bone conduction thresholds with or without a 10% or greater change in speech discrimination score (sensorineural change), or a change of 10% or more in speech discrimination score alone. Results of therapy were considered successful if there was no change in hearing or a significant improvement in hearing. Therapy was judged to have failed if hearing became significantly worse.

The success rate for the results of therapy on hearing for the ears in the five groups was high and similar (Table 6). In all five groups there were ears that had a significant change in speech discrimination without a significant change in air or bone conduction thresholds (Table 7). In groups II, III, and V, there were hearing changes of both the conductive and sensorineural types. In group I, the changes in hearing were of the conductive type. However, as would be expected, in group IV, all the changes in hearing were of the sensorineural type. Thus, it seems obvious that, in a small but significant percentage of patients with otosclerosis, a combination of calcium gluconate, sodium fluoride, and vitamin D can reverse either a conductive or a sensorineural hearing loss.

For the ears in each of the five groups, very little change in ear air conduction thresholds, bone conduction thresholds, or speech discrimination scores took place between the pretreatment tests and the last posttreatment tests (Table 8).

During treatment with calcium gluconate, sodium fluoride, and vitamin D, hearing either did not change or was improved in a high percentage of ears in the five groups of patients with otosclerosis. However, the duration of therapy has been relatively short. A small but significant percentage of patients had reversal of a conductive hearing loss or a sensorineural loss or had improvement in speech discrimination. The fact that most of these hearing impairments were of a progressive type and not expected to have spontaneous im-

TABLE 7. CHANGES IN HEARING IN PATIENTS WITH OTOSCLEROSIS

		No. of Ears with Hearing Changes					
	No. of	*Conductive*		*Sensorineural*		*Speech Discrimination*	
Group	*Ears*	*Improved*	*Worse*	*Improved*	*Worse*	*Improved*	*Worse*
I	15	4	8	0	0	3	0
II	32	7	6	5	2	6	6
III	54	4	3	9	11	17	10
IV	42	0	0	13	12	13	4
V	9	1	4	0	2	0	2
Total	152	16	21	27	27	39	22

TABLE 8. RESULTS OF THERAPY IN PATIENTS WITH OTOSCLEROSIS AND HEARING LOSS

Group	*No. of Ears*	*Mean Change (dB/ear)**		*Mean Change in Speech Discrim. (%)*
		ACT	*BCT*	
I	51	−1.1	−1.6	+2.0
II	109	+1.4	+0.3	+0.5
III	167	−0.3	−0.9	+0.7
IV	132	+0.3	+1.2	+2.3
V	46	−2.1	−1.9	−2.3

*Minus (−) means depression in hearing; plus (+) means improvement in hearing.

ACT - Air conduction thresholds; BCT - Bone conduction thresholds.

provement is rather compelling evidence for the efficacy of the therapy.

SIDE EFFECTS OF THERAPY

Information was available on 343 patients in this study as to the incidence and types of adverse side effects that can be associated with the ingestion of calcium gluconate, sodium fluoride, and vitamin D. Two hundred and eighty-two (82%) patients experienced no problems taking the medications. The remaining 61 (18%) patients had various degrees and types of difficulties. The most frequent side effects were gastrointestinal symptoms usually directly related to the ingestion of sodium fluoride. These symptoms occurred in 47 (14%) patients. Nineteen patients had mild intermittent nausea, and three patients had mild intermittent heartburn but continued taking the medications. Six patients who had rather severe heartburn and three patients who had persistent nausea associated with the ingestion of sodium fluoride capsules had no problems taking sodium fluoride enteric-coated tablets. Thus, 313 (91%) patients could take medications.

However, 16 (5%) patients stopped taking the medications because of severe and persistent gastrointestinal symptoms. Ten patients experienced severe persistent nausea, and one also had vomiting. Two patients stopped taking the medications because of heartburn, three patients because of diarrhea, and one patient because of loss of appetite.

The second most frequent side effect of therapy was musculoskeletal pain, which occurred in 10 (3%) patients. Nine patients stopped taking the medications because of joint pain. One of these patients had ankle pain and edema. The remaining patient stopped the medications because of diffuse muscular pain. In all patients, pain stopped completely shortly after discontinuing the medications.

One patient discontinued medications because of ankle edema and another because of light-headedness. However, the latter patient had light-headedness before therapy, and the symptom probably was not related to the ingestion of the medications.

Two (0.6%) patients developed renal calculi while on the medications, one after 6 months of therapy and the other after 14 months of therapy. The renal calculi may have been related to therapy, but this problem has not been encountered in more than 300 additional patients treated.

Two patients in this study developed renal calculi while receiving calcium gluconate, sodium fluoride, and vitamin D. However, this probably was a coincidence. Otherwise, there were no serious or irreversible adverse side effects of therapy. Actually, several patients who had to stop the medications because of nausea and heartburn probably could have continued taking them if the sodium fluoride enteric-coated tablet was still available.

EFFECT OF THERAPY ON CERTAIN FACTORS IN THE BLOOD

Possible effects of the ingestion of calcium gluconate, sodium fluoride, and vitamin D on the blood levels of calcium, phosphorus, alkaline phosphatase, creatinine, and parathyroid hormone were investigated (Table 9). With the exception of parathyroid hormone determinations, blood levels were determined in most patients before therapy and after various durations of therapy and compared. Parathyroid hormone values were not determined before treatment and only after rather long durations of ther-

TABLE 9. EFFECT OF THERAPY ON BLOOD LEVELS IN PATIENTS WITH OTOSCLEROSIS

Test	*No. of Patients*	*Duration of Therapy (mo)*		*Results of Test*			
				Normal		*Abnormal*	
		Mean	*Range*	*No.*	*%*	*No.*	*%*
Calcium	101	20	4-44	101	100	0	0
Phosphorus	97	20	4-44	97	100	0	0
Alkaline phosphatase	97	20	4-44	92	95	5	5
Creatinine	83	18	4-44	81	98	2	2
Parathyroid hormone	25	26	17-44	25	100	0	0

apy. Normal levels were found for calcium in the 101 patients studied, for phosphorus in the 97 patients, and for parathyroid hormone in the 25 patients. Normal levels were found for 92 of the 97 patients tested for alkaline phosphatase. In the remaining five (5%) patients, levels were elevated above the normal range and above the pretreatment values. However, most of these elevations in alkaline phosphatase levels were not significant. Normal levels were found for 81 of the 83 patients tested for creatinine. In the remaining two (2%) patients, levels were not significantly elevated above the normal range and the pretreatment values.

This investigation indicates that the ingestion of calcium gluconate, sodium fluoride, and vitamin D in the doses and for the durations described has no significant effect on the blood levels of calcium, phosphorus, alkaline phosphatase, creatinine, and parathyroid hormone.

DISCUSSION

Five groups of patients with otosclerosis were analyzed. The first four groups consisted of 500 patients classified according to the relative and absolute amounts of sensorineural hearing loss in the hearing-impaired ears. The patients in group V were selected because they had bilateral hearing loss, they had had a prior unilateral stapedectomy for otosclerosis, and they had received medical therapy for otosclerosis.

Whether or not the entity of pure labyrinthine otosclerosis exists is controversial. In other words, can otosclerosis produce a sensorineural hearing loss without stapes fixation? The patients in group IV all had pure labyrinthine otosclerosis. The other four groups had clinical evidence of stapes fixation. In this study, evidence was sought that would either refute or support the existence of pure labyrinthine otosclerosis. There were considerable similarities between the patients in group IV and the patients in the other four groups. Most of the patients in group IV were females, as was true for the other groups, with the exception of group III, in which the sex incidence was about equal. In all groups, most of the patients had family histories of hearing loss. In addition, in each group, a significant number of patients had family histories of otosclerosis, the incidence being similar in group IV (11%) and group V (11%). Most of the patients in the first four groups had bilateral hearing impairment. The patients in group V were selected because they had bilateral hearing loss. Some patients in each group had ears that had fluctuation in auditory acuity. The incidence was slightly higher in group IV, but the incidence of fluctuation in auditory acuity tended to increase as the relative and absolute amounts of sensorineural hearing loss increased. The responses of the patients in group IV to calcium gluconate, sodium fluoride, and vitamin D in regard to relief of vestibular symptoms and the stabilization of hearing were similar to the responses of the patients in the other groups. In addition, a small but significant number of patients in each group had progressive hearing loss that was reversed by medical therapy. For these reasons, as well as the demonstration of the reversal of roentgenographic changes consistent with otosclerosis in the otic capsule by medical therapy in ears with pure sensorineural hearing loss, we believe that pure labyrinthine otosclerosis is a definite entity. The diagnosis of pure labyrinthine otosclerosis is dependent on the demonstration of changes in the otic capsule consistent with otosclerosis by 1-mm cut compound motion tomography, and here there can be a significant problem in interpretation. No problem exists when the roentgenographic changes consistent with otosclerotic involvement of the otic capsule are pronounced or when roentgenographic changes suggestive of otosclerosis are absent. However, a significant number of patients with sensorineural hearing loss have roentgenographic changes in the otic capsule that are only minimally suggestive of otosclerosis, and thus, a diagnosis of this condition is uncertain.

Six types of vestibular symptoms were experienced by the patients in groups I through IV. These vestibular symptoms consisted of recurrent spontaneous attacks of vertigo, recurrent spontaneous attacks of imbalance, postural vertigo, postural imbalance, a single spontaneous episode of vertigo, and a single spontaneous episode of imbalance. This study demonstrated that the incidence of vestibular symptoms in patients with otosclerosis increased as the relative and absolute amounts of sensorineural hearing loss increased and was far higher than one would expect in the normal population. The incidence progressively increased from 26% in group I to 57% in group IV. In addition, the severity of vestibular symptoms increased and the incidence of demonstrable vestibular abnormalities on the bithermal caloric test in those patients with vestibular symptoms increased with increasing sensorineural hearing loss. The correlation between inner ear hearing impairment and the incidence and severity of vestibular symptoms indicates that the vestibular symptoms are due to the otosclerotic process.

The effects of calcium gluconate, sodium fluoride, and vitamin D on vestibular symptoms experienced by patients in groups I through IV and on hearing impairment in patients in groups I through V were investigated. The mean duration of therapy for the groups was relatively short, varying from 13 to 16½ months, and thus, this can be considered as a preliminary report. Satisfactory control (complete control or improvement of 50% or more) of both recurrent spontaneous attacks of vertigo and recurrent spontaneous attacks of imbalance was achieved in a high percentage of the patients experiencing these symptoms in each group. If the patient episodes of recurrent spontaneous attacks of vertigo and imbalance are lumped together, then 100% of these episodes were satisfactorily controlled in group I, 91% in group II, 90% in group III, and 87% in group IV. In addition, satisfactory control of postural vertigo and postural imbalance was achieved in a relatively high percentage of patients in groups I to IV experiencing these symptoms. A higher percentage of patients achieved satisfactory control of postural vertigo than of postural imbalance. If the patient episodes of postural vertigo and postural imbalance are lumped together, then 70% of these episodes were satisfactorily controlled in group I, 100% in group II, 59% in group III, and 61% in group IV. Even though this is a preliminary report, these impressive statistics make it logical to conclude that a combination of calcium gluconate, sodium fluoride, and vitamin D has a beneficial effect in controlling vestibular symptoms experienced by patients with otosclerosis and, thus, in controlling the disease process.

During treatment with calcium gluconate, sodium fluoride, and vitamin D, hearing did not change or was improved in a high percentage of ears in the five groups of patients with otosclerosis. The incidence of a successful hearing result was 84% in group I, 87% in group II, 86% in group III, 88% in group IV, and 83% in group V. A small but significant percentage of patients had reversal of a conductive hearing loss or of a sensorineural hearing loss or had improvement in speech discrimination. The fact that most of these hearing impairments were of a progressive type and not expected to have spontaneous improvement is rather compelling evidence for the efficacy of the therapy.

Information was available on 343 patients in this study as to the incidence and types of adverse side effects that can be associated with the ingestion of calcium gluconate, sodium fluoride, and vitamin D. Eighty-two percent of the patients experienced no problems while taking the medications. An additional 9% of the patients had gastrointestinal symptoms but continued to take the medications because the symptoms were mild or intermittent or because the symptoms did not occur when sodium fluoride capsules were replaced by enteric-coated tablets. Nine percent of the patients had to discontinue medications because of side effects. The most frequent side effect was gastrointestinal symptoms, followed in frequency by musculoskeletal pain. These symptoms associated with medical therapy promptly stopped after the discontinuation of the medications. Two patients (0.6%) developed renal calculi while on therapy. The renal calculi may have been related to therapy, although this problem has not been encountered in more than 300 additional patients treated. The ingestion of calcium gluconate, sodium fluoride, and vitamin D in doses described under "Methods and Materials" had no significant effect on the blood levels of calcium, phosphorus, alkaline phosphatase, creatinine, and parathyroid hormone. Thus, there would seem to be no contraindication to this medication in the treatment of healthy adults with otosclerosis.

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PERILYMPH FISTULAS

DIAGNOSTIC CRITERIA AND THERAPY

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Fifty-one patients suspected of having a perilymph fistula were evaluated. We postulated that many patients with predominantly vestibular complaints had unrecognized perilymph fistulas. An analysis was made of symptoms, physical findings, vestibular and audiometric test results in order to determine appropriate diagnostic criteria for the presence of perilymph fistulas. The patient population was divided into two groups, those with and without fistulas. Data from both groups were compared by mean values of variables, step-wise discriminant analysis, and factor analysis. A history of trauma with sudden onset of dizziness and/or hearing loss should alert the physician to a fistula. Findings of significance were positional nystagmus of short latency and long duration without import of nystagmus direction, canal paresis and reduced speech reception threshold with poor speech discrimination scores. Discriminant analysis correctly classified 19 fistula and 10 nonfistula cases explored operatively and identified two error judgments in 22 nonoperated cases. Bed rest for the first five days proved to be the most effective means of therapy. Surgical intervention with repair of the fistula by perichondrial graft provided effective control of vertigo more frequently than restoration of hearing.

Perilymph fistulas, be they of congenital, poststapedectomy or spontaneous origin, continue to present diagnostic and therapeutic problems to the otologist. The matter was simple and of little consequence when only the occasional congenital fistula presented itself. The advent of stapedectomy procedures led to many more fistulas and the need to develop appropriate diagnostic criteria. Perilymph fistula was recognized as one of the most serious and common complications of the stapedectomy.[1-5] The diagnostic picture became more complex when Simmons first theorized that ruptures of the membranous labyrinth would likely lead to sudden deafness, as in the 15 cases he presented.[6] Shortly thereafter, Fee presented the first three cases of traumatic oval window fistulas, not associated with stapedectomies.[7] Subsequently, Stroud and Calcaterra presented four additional cases of perilymphatic fistulas occurring at the oval window and felt that increased intracranial pressure was the responsible agent in three of the cases.[8] Goodhill then reported cases of round window fistulas also with sudden hearing loss.[9]

As case reports began to build up it became apparent that fistulas could occur with sudden hearing loss alone or with sudden hearing loss and vestibular symptoms as well. Healy et al in 1975, reported on a group of 40 perilymph fistula patients in which mention was made of cases where vertigo occurred alone without hearing loss.[10] It was in early 1976 that we became aware of this fact and recognized that in our patient population we had three cases that were quite similar to the ones Healy described. Exploration of those three cases documented clear-cut perilymph fistulas with vertigo as the only symptom, and led to our current interest in defining the diagnostic criteria and therapeutic regimen for patients with perilymph fistulas. Additional cases of fistulas without hearing loss have been described by Kohut et al.*

We postulated that the symptoms and findings of patients with perilymphatic

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*Kohut RI, Waldorf RA, Thompson JB, et al: Minute perilymph fistulas: vertigo and Hennebert's symptom without hearing loss (operative indications). Unpublished data.

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TABLE 1. MEAN SCORES OF MOST SIGNIFICANT VARIABLES

Variables	*Non-Fistula Group (%)*	*Fistula Group (%)*
Historical		
Age	43.2 yr	46.6 yr
Sex, female	65	50
*Trauma	59	82
*Sudden onset	71	82
Dizzy	88	94
Nausea and vomiting	29	32
*Tinnitus	59	62
Auditory		
Hearing loss	35	38
*†SRT	88	150
Speech discrimination	6	32
Electronystagmography		
*Fistula test	18	26
*†‡Canal paresis	112	91
Directional preponderance	41	47
Caloric pattern	35	9
Spontaneous nystagmus	18	15
*Right/left gaze	6	24
Pendulum	18	15
*Positional nystagmus	94	94
*Supine	35	59
Up straight	35	29
*Right ear down	47	62
Up straight	29	41
Left ear down	35	29
Up straight	29	32
*Head hanging	29	44
*Up straight	24	47
*Head hanging right	29	53
Up straight	24	29
Head hanging left	59	62
Up straight	29	44

*Significant factors in discriminant analysis; †Weighted scores - severity; ‡Indicative of nonfistula.

fistulas should be similar regardless of location (round or oval window). We also postulated that a chief complaint of either hearing loss or dizziness would not alter the other findings. We presumed the etiology of the fistula should make little difference to the findings whether it was congenital, poststapedectomy, fracture, or pressure change. We recognized that a loose prosthesis could cause varying symptoms dependent on location and independent of fistula findings.

This paper will not deal with the mechanisms of rupture of the inner ear membranes, nor the anatomical or physiological reasons for rupture and healing. If the reader is unfamiliar with these topics he is referred to articles by Goodhill,[9] Stroud and Calcaterra,[8] Axelsson et al,[11] Simmons,[*][6] and Ivarsson and Pedersen.[12]

METHODS AND MATERIALS

A group of 51 patients suspected of having perilymphatic fistulas were studied, diagnosed, treated and followed for a minimum of 90 days. There were 34 fistula cases, 19 proved surgically and 15 diagnosed and treated medically. The control group consisted of 17 cases, 10 proved surgically, 8 by tympanotomy and 2 by mastoidectomy. The controls consisted of two patients with bony fistulas only, six with benign paroxysmal postural vertigo, two with cerebral concussion, two early Ménière's cases, two vestibular neuronitis, two with sudden hearing losses, two with inner ear adhesions to the stapes prosthesis (vestibulofibrosis) and one malingerer complaining of sudden deafness and unsteadiness, neither of which could be documented.

We emphasize that the control group was not chosen from a normal population. The nonfistula patients were matched as closely as possible on age, hearing loss, symptoms and positional nystagmus. Both groups also had similar histories of trauma and sudden onset of symptoms. Table 1 shows that positional nystagmus was seen in 94% of both groups and dizziness occurred in at least 88% in both groups. Hearing loss had similar incidence in both groups as well as many other similarities between the fistula and nonfistula patients.

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[*] Simmons FB: The double membrane break syndrome in sudden hearing loss. Unpublished data.

Our regimen of evaluating any patient suspected of having a perilymph fistula was to obtain a complete and detailed history of trauma from head blow, increased intracranial or external pressure, including loud noises or prior surgical intervention, particularly stapedectomy of the ear. Each patient was asked to fill out a dizziness questionnaire so that fine points of history were not missed. Patients were queried carefully about prior venereal disease exposure, particularly gonorrhea during World War II. In addition to the usual general ear, nose and throat evaluation, a complete neurological work-up involving the cranial nerves and cerebellum was carried out. Audiometric evaluation included as a minimum, pure tone air and bone curves, speech reception threshold and discrimination scores. Originally, additional tests were used for completeness but subsequently were dropped. The electronystagmogram included a study of saccades, gaze, smooth eye pursuit, positional testing, fistula test with positive and negative pressure and caloric evaluation. Radiographic views were obtained of the internal auditory meati. Polytomography of the petrous pyramid was obtained if there were abnormalities of the internal canals or if there was history of significant trauma to the head which might produce fractures.

Fifty-nine variables of history, physical findings, audiometry and electronystagmography including positional nystagmus, were evaluated in each of the 51 cases. The mean value of the 31 variables felt to be significant was calculated and tabulated. Step-wise discriminant analysis using the BMD# O7M Biomedical Computer Program was carried out using the 31 variables on the 19 proven fistula cases versus the 10 proven nonfistula cases.[13] The nonoperated fistula and control patients were then added to the program and studied as well.

Factors were deleted because they added no significant information to either identifying fistula patients from the normal population or from the fistula control group. The audiometric variables dropped included Békésy, SISI, tone decay, tympanometry, and stapedial reflexes. Additional data from the positional testing was dropped such as direction and severity of the nystagmus and presence of subjective dizziness. The directional information was felt to be valuable but this program was not able to handle it appropriately.

Factor analysis using the BMD#O8M Biomedical Computer Program was used to assist in recognizing the factors contributing to the variance between the control and fistula groups.[13]

Data from the surgically repaired fistula patients were gathered and analyzed relative to the success or failure of the various graft materials used to successfully close the fistula and have it remain closed.

RESULTS

Mean Values. The information listed in Table 1 compares the mean values for the 31 variables felt to be significant in the fistula and nonfistula groups. The asterisked items are those which 1) raise suspicion of a fistula because of their high incidence and 2) help differentiate the fistula case from one quite similar. Trauma, as used here, includes patients who have had stapedectomies, those with head blows, and those who have experienced sudden intracranial or external pressure change. The weighting of females in the nonfistula group is felt to be coincidental. The values for speech reception threshold and canal paresis were weighted values dependent upon severity or magnitude. All of the rest of the values represent simple "yes" or "no" as to the presence of the variable.

It would appear that there are significant differences between the two groups, when one considers positional nystagmus in the supine, right ear down, up straight after right ear down, head hanging, up straight after head hanging, and head hanging right positions. Nystagmus in these positions is strongly suggestive of a fistula. A complete analysis of the significance of each of the characteristics of positional nystagmus including direction, magnitude, relation to involved ear, latency and duration will have to await further investigation.

Positional nystagmus occured with the involved ear down in 26 of 34 cases. The nystagmus was in the same direction as the involved ear in 14 of the 26 cases where it occured with that ear down. In some instances the direction differed between ear down and head hanging. Canal paresis occurred on the same side as the lesion in 12 cases and on the opposite side in 6 cases. There were equal numbers of left and right ears involved.

The positional nystagmus that occurs in the presence of a fistula can be characterized as follows:

1) There is short or no latency present.

2) The nystagmus is not as violent as that usually seen in benign paroxysmal postural vertigo.

3) The duration is usually long.

4) The nystagmus fatigues slowly or not at all.

5) The nystagmus rarely reverses direction on changing from a head down or head hanging position to a sitting position.

6) The nystagmus does not necessarily beat toward the involved ear.

7) The nystagmus usually occurs with the involved ear down.

8) The nystagmus is only occasionally rotatory.

From the information listed in Table 1, one would become highly suspicious that a fistula was present if the patient had a sudden onset of postural vertigo and/or hearing loss after trauma with positional nystagmus not fitting any clear-cut pattern but being present in several positions. The presence of right or left gaze nystagmus, a normal caloric pattern, reduced speech reception threshold, and discrimination scores lower than expected would further confirm the diagnosis.

Note that the positive fistula test was present in only 26% of the fistula cases and was present in 18% of the nonfistula. By the term positive fistula test, we mean eye deviation or nystagmus after either positive or negative pressure applied to the ear. Care must be exercised not to create a cold air caloric when performing the fistula test. Even though a positive fistula test was present in three nonfistula cases, we feel this finding warrants treatment as a fistula.

Step-Wise Discriminant Analysis. The use of discriminant analysis accurately separated the 19 operated fistula cases from the 10 operated controls as would be anticipated. When all nonoperated patients were placed in each group, two cases were identified as being misclassified, one each from the nonfistula and fistula groups.

The variables identified as most significant in separating the controls from the fistula group included dysrhythmia of the caloric pattern, canal paresis, right/left gaze nystagmus, trauma, positive fistula test and positional nystagmus in the right ear down, right head hanging, or supine positions. The sequence in order of importance of the variables would change slightly from time to time as new members were added to the patient population, either in the control or fistula group.

Our review of the two cases that the program rejected would suggest they were appropriately rejected. One was a young college girl, severely beaten and unconscious for several hours, who was classed as a fistula. As time passed it was fairly clear that she had residual central nervous system damage and not a fistula. The other was a college girl who fell from her bicycle, was knocked unconscious and developed what we thought initially was a benign paroxysmal postural vertigo from head blow. She refused to follow bed rest advice in the beginning, developed influenza some two weeks later and was bedridden for five days. At the end of bed rest her dizziness was completely clear.

Factor Analysis. Factor analysis was used to help recognize those groups of variables which fell together to help identify the variances between the two groups. In order of prominence, these included right ear down and up straight after right ear down positional nystagmus, hearing loss including poor discrimination scores and speech reception thresholds, head hanging right and up straight after head hanging right. The presence of positional nystagmus with the left ear down and up straight after left ear head hanging are negative factors for a fistula as is the presence of spontaneous nystagmus associated with right and left gaze nystagmus.

Medical Care. Patients seen early after the onset of their symptoms were placed on absolute bed rest with the head of the bed elevated 30° to 40° for five days. They were sedated and placed on stool softeners. Hearing was evaluated at three days and five days. Positional testing was done at five days. Only supine, right and left ear down positions were used. Head hanging positions were omitted. The patient was assisted back into the sitting position so that there was little abdominal pressure increase. If symptoms were clear at that point, the patient was sent home for ten days of additional recovery with limited activity: still sleeping with the head of the bed elevated, doing no lifting or straining and staying on stool softeners. The next two weeks the patient was allowed to return to light duty work.

Of the 15 patients so treated, 9 cleared their symptoms completely; 2 cleared, reruptured, and cleared again on bed rest. One cleared all of the vertiginous symptoms, but only a portion of the hearing symptoms, and three failed to respond to therapy.

Surgical Care. Surgical intervention in the form of exploratory tympanotomy of the involved ear was carried out if medical therapy failed or if the patient had symptoms for over one month. Tympanotomy was carried out under local anesthesia with careful control of bleeding as the tympano-meatal flap was developed. First the round window and then the oval window were evaluated carefully before any curetting was done in the region of the scutum. Care was taken not to avulse adhesive bands as a serous leak would occur, making it difficult to recognize a fistula. The work of Arnold would suggest that lysing such adhesions might in itself create a perilymph leak.[14] Fistulas not readily apparent could be demonstrated by having the patient perform a Valsalva maneuver, by pumping the stapes, or by lowering the head of the patient. Only after these maneuvers were carried out, were any mucosal bands or folds cut to obtain a better view of the two windows.

If a fistula was found, the area about the fistula was denuded of mucosa. For round window fistulas, the bony overhang was drilled away from complete exposure. A small perichondrial graft from the tragus was applied to the denuded area and packed in place with Gelfoam®. The ear was closed and the patient placed on absolute bed rest and the remainder of the medical care regimen. Patients with oval window patch failures were treated with stapedectomy or prosthesis removal and complete oval window perichondrial seal under a new prosthesis.

In the majority of oval window fistulas the perilymph leak was found at the anterior portion of the footplate of the stapes. A typical case with a large rent anteriorly in the annular ligament is illustrated in Figure 1. Figure 2 depicts repair of this fistula with perichondrium. Most of the leaks involving the round window were located at the margin of the window. Round window leaks were generally small and difficult to see. There were 8 round window and 12 oval window fistulas (one patient had both).

The results of surgical intervention were as follows: of the 19 patients operated, 3 had complete recovery from vertigo and restoration of hearing. Seven had recovery of vertigo but no improvement of hearing. This group of patients supports Simmons' theory espoused in his recent, unpublished work that a round or oval window fistula may be closed with resultant clearing of vestibular symptoms but little or no recovery of hearing.* Five cleared their vertiginous symptoms who had no hearing loss prior to surgery, two had marked improvement in vertigo who had no hearing loss prior to surgery and two patients healed

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*Simmons FB: The double membrane break syndrome in sudden hearing loss. Unpublished data.

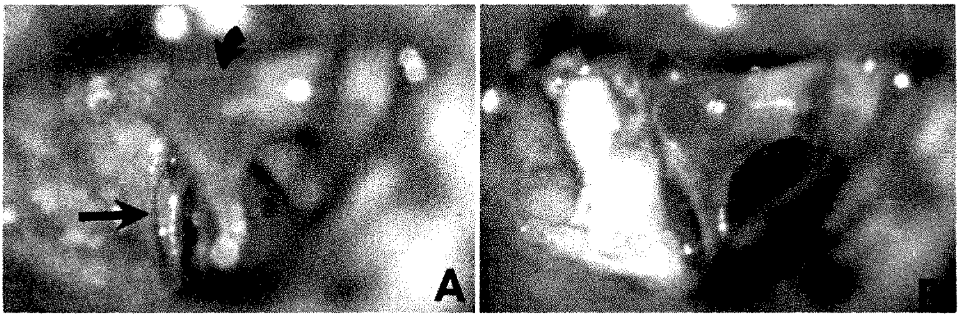

Fig. 1. A) Typical fistula with large rent anteriorly in the annular ligament (straight arrow); lenticular process of the incus (curved arrow). B) Repair of fistula with perichondrium.

and reformed the fistula on exertion months later. Both are scheduled for future surgery. Neither of these failures responded to bed rest. The two patients with marked improvement had closure of the fistula and the minor imbalance remaining was due to severe cerebral concussion.

There were 9 surgical failures among the 19 operated fistula cases. Four failed, were repaired with a different graft material and have remained healed. Two failed and have yet to be repaired. Two had labyrinthectomies done after failure since they had no useful hearing in the ear and one had a labyrinthectomy following the development of a granuloma.

An evaluation of the graft materials used is of value in understanding the surgical failures. Seven patients were repaired with fat grafts, six of these failed. Three were secondarily repaired with perichondrium and two had labyrinthectomies. Two of the eight perichondrium grafts failed. One, eight weeks postoperatively and the other, one week postoperatively when the patient developed an acute URI and had a bout of sneezing. One of these was repaired with a fascia graft which has held. Two patients were repaired with Gelfoam®, one of these developed a severe granuloma that required labyrinthectomy after the patient refused early surgical intervention.

SUMMARY AND CONCLUSIONS

The step-wise discriminant analysis approach was an extremely effective means of identifying suspected cases of fistula. To make the diagnosis of a perilymph fistula, one must have a high index of suspicion of every patient who presents with a history of sudden onset of positional vertigo and/or hearing loss, particularly after some sort of traumatic episode. Spontaneous nystagmus in conjunction with right and left gaze nystagmus suggested that a fistula was not present. However, gaze nystagmus alone occurred in one fourth of the fistula patient population. Positional nystagmus occurring in the supine, right ear down and head hanging right positions, was more likely to occur in our series with fistulas than with similar cases (controls). Positional nystagmus usually begins after little or no latency. It is quite long-lasting but not terribly severe. Fatigue is slow, if at all, and is likely to occur with the involved ear down, though not necessarily beating toward it. Nystagmus rarely reverses direction on sitting up. Even though the fistula test was only positive in one fourth of our cases, and has been reported in only a low percentage of other series, its presence is a strong indication of a fistula.[4,8-10]

It was apparent from our results and those of others, that bed rest with the head elevated, and avoidance of increased intracranial pressure, resulted in better recovery than surgical intervention. Failure to respond to bed rest or in cases of long-standing fistula, surgical intervention was indicated. Certainly, in our hands, perichondrium proved to be the superior graft material and was the choice of others.[9]

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FIFTH BRITISH ACADEMIC CONFERENCE IN OTOLARYNGOLOGY

The Fifth British Academic Conference in Otolaryngology will be held July 22-27, 1979, at the University of Birmingham (U.K.). Master will be Sir Geoffrey Bateman, MA, FRCS. This conference has academic and scientific programs with distinguished international contributors to discuss a wide range of modern developments within the specialty.

Morning plenary sessions will be held with papers from invited speakers. Open panel discussions will be a significant feature and instructional sessions will also take place as well as audiovisual programs. Finally there will be a scientific and trade exhibition.

For further information and application forms write: V. Hammond, FRCS, 55 Harley Street, London WI, England.

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EUROPEAN CONGRESS OF PAEDIATRIC OTOLARYNGOLOGY

The Section of Paediatric Otolaryngology of the Polish Otolaryngological Society announces the First European Congress of Pediatric Otolaryngology to be held in Warsaw October 5-7, 1979. Applications are to be sent to the Congress Secretary: Dr. hab. M. Goralowna, MD, ul Neilkanska 4/24, Children's Hospital, 03-924 Warszawa, Poland.

Ann Otol 87:1978

HYPERCHOLESTEROLEMIA AND AUDITORY DYSFUNCTION

EXPERIMENTAL STUDIES

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Michael M. Paparella, MD
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Rabbits were used for the long-term study of auditory function associated with experimental hypertension and hypercholesterolemia. Auditory dysfunction (threshold changes of sound evoked responses) was monitored with an electrode, chronically implanted into the contralateral inferior colliculus. Hypertension was created using the renal encapsulation technique. Auditory function in the hypertension trial demonstrated a dip at higher frequencies as well as improvement at lower frequencies. One gram of cholesterol fed daily for three months was capable of making rabbits atherosclerotic. Cholesterol-fed rabbits showed increasing auditory dysfunction over time at all frequencies. When experimental hypertension was combined with hypercholesterolemia, the auditory changes appeared additive. This work, although in preliminary stages, seems to provide experimental evidence that auditory dysfunction is associated with cholesterol diet.

Many authors have described vascular causes of sensorineural hearing loss (SNHL) and empirical treatment for such patients. Clinical hearing problems with an alleged vascular base include sudden and progressive SNHL such as 1) sudden deafness, 2) leukemic deafness, 3) vascular obstruction, 4) diabetes mellitus, and 5) presbycusis, where arteriosclerosis and/or atherosclerosis has been implicated.

Scientific validity for the treatment of vascular problems in SNHL is lacking; however, research suggests important relationships between vascular phenomena and auditory dysfunction. Temporal bone histopathological documentation of vascular problems is preliminary at the present; further studies are necessary. In a previous study of 42 temporal bones of leukemic patients, leukemic infiltrations were described in the middle and inner ears. Although progressive hearing loss was seen in some patients, profound hearing loss occurred as a terminal event in which inner ear hemorrhage was seen (Fig. 1). Vascular obstruction as a cause of hearing loss is best demonstrated in animals (Fig. 2A) and can be intimated in humans (Fig. 2B). We recently surveyed our temporal bone cases of presbycusis and diabetes mellitus for obvious vascular changes using light microscopy. None was found.

A number of otophysiological laboratory studies of vascular phenomena and their possible influence on measured audition have been initiated.

Cochlear blood volume studies were done in guinea pigs, using Cr^{51} labelled red blood cells.[1] This method provided basic data for the study of oxygen requirement in the cochlea. The method can be applied for the study of altered vascular phenomena. Anemia was experimentally induced in 22 guinea pigs with phenylhydrazinehydrochloride and temporary high frequency losses in the cochlear microphonics (CM) and reduction in endocochlear DC potential (EP) were noted.* Vascular perfusion studies dem-

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*Morizono T: The effect of chronic anemia on cochlear function. Unpublished data.

From the Otophysiology Research Laboratory, Department of Otolaryngology, University of Minnesota, Minneapolis, Minnesota. Funded by a grant from NIH (NS 12125-03), a research grant from the Deafness Research Foundation, and NHMRC research grant from the Commonwealth of Australia.

Presented at the meeting of the American Otological Society, Inc., Palm Beach, Florida, April 23-24, 1978.

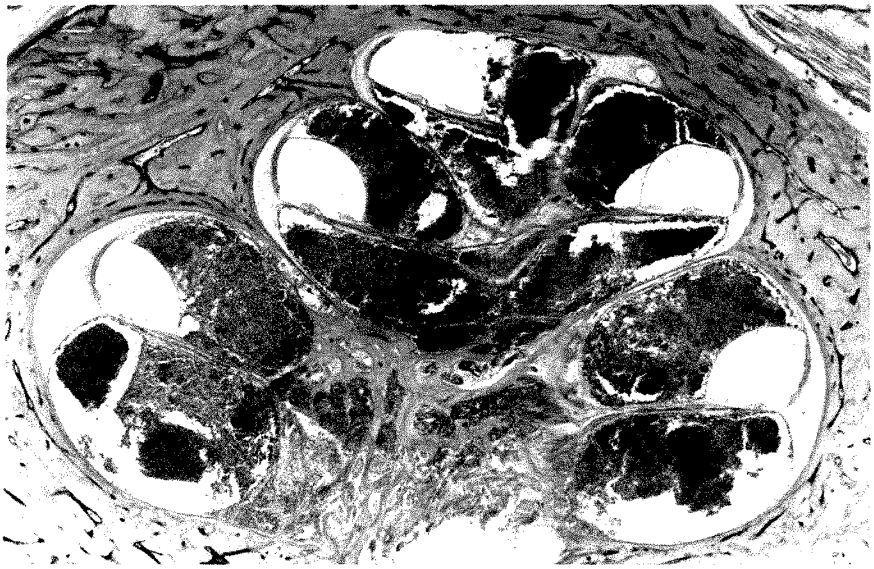

Fig. 1. Midmodiolar section of patient with profound deafness and terminal leukemia. Leukemic hemorrhagic infiltrates are seen throughout the perilymphatic scalae with hydrops of the endolymphatic space. (H & E, × 20)

onstrated the ability to maintain CM by perfusing artificial blood. The CM correlated with the oxygen supply of the cochlea which was varied by changing the hematocrit and the flow rate of the perfusate independently.[2] Stimulation of the hypothalamus or intense sound stimulation in cats resulted in measureable changes in cochlear blood flow.[3] In this study, we describe methods and preliminary experimental results for hypertension and hypercholesterolemia using chronic animal models.

The hypotheses or research questions are: 1) Does hypertension result in measurable auditory dysfunction? 2) Does a long term cholesterol-rich diet lead to measurable auditory dysfunction? 3) How does a combination of hypertension and hypercholesterolemia influence auditory function?

LITERATURE SURVEY

Hypertension and Hearing. Rosen et al[4,5] showed that there was a simultaneous occurrence of hypertension and hearing loss for high tones, whereas for primitive tribes in the Sudan neither blood pressure nor hearing loss were increased with age. This pointed to a possible link between hypertension and hearing loss. Studies in part indicated that hypertension and perceptive hearing loss have no correlation.[6-8] According to Hansen,[9] a raised blood pressure per se, without an involvement of central auditory pathways, does not seem to affect hearing.

Hypercholesterolemia and Hearing. It is a well-accepted fact today that the serum cholesterol level is a most important and related factor in determining an individual's risk of developing atherosclerotic coronary disease, i.e., the higher the serum cholesterol, the greater the risk.[10,11]

Atherosclerosis, manifested in the lipid-containing intimal lesions of small and large arteries, is the most common pathological form of vascular disease and the most detrimental in its effect on the blood and oxygen supply to any given organ according to Katz and Pick.[12]

Epidemiological studies conducted by Rosen and his colleagues[4,5,13,14] revealed the strong link between high blood cholesterol levels, coronary heart disease, and deteriorated hearing. Douglas[15] postulated a possible link between Ménière's disease and decreased

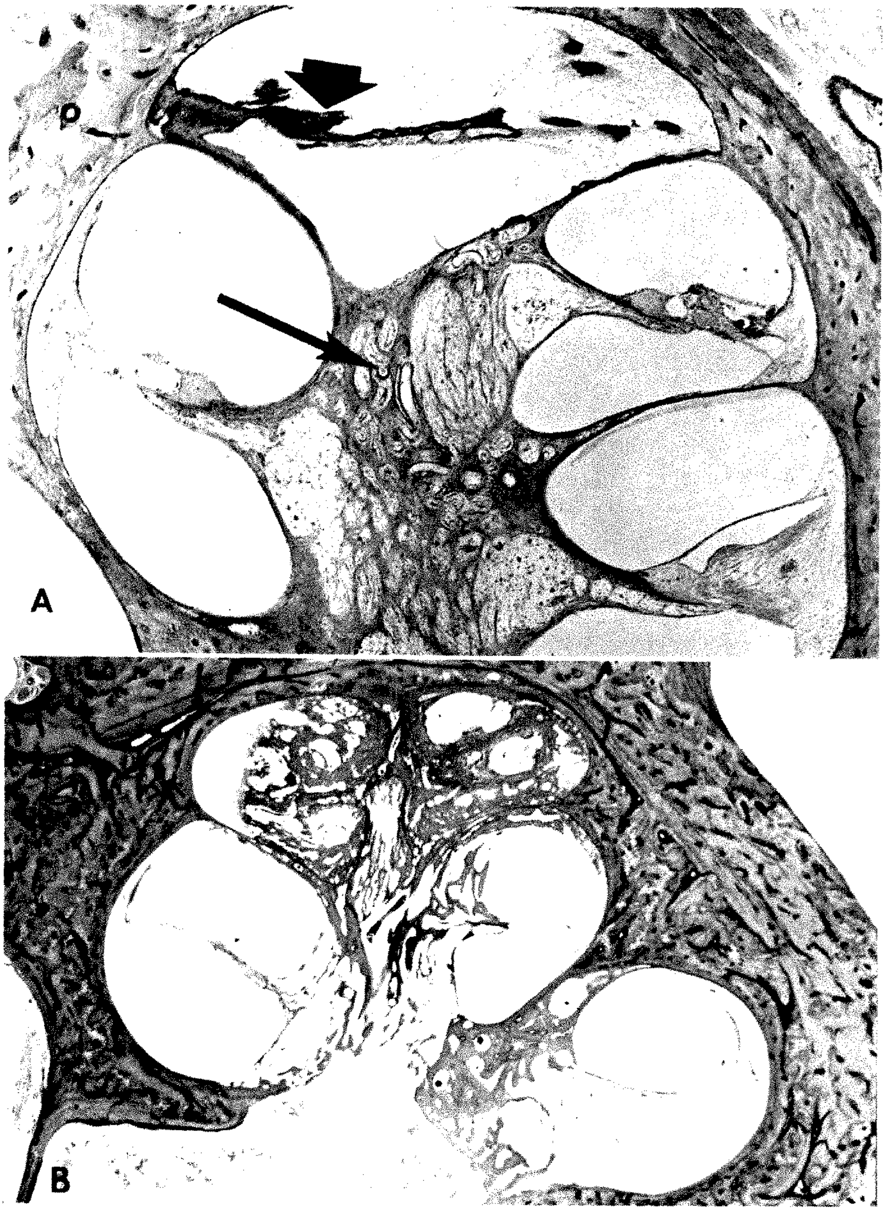

Fig. 2. Animal and human examples of microembolization. A) Cat temporal bone 12 months after experimental microembolization using styrene divinylbenzene copolymer beads (12 to 35 μ) in modiolus (thin arrow) shows fibrosis and new bone formation in apex (thick arrow). Organ of Corti changes and loss of spiral ganglion cells are seen. (H & E, X 20) B) Human case of meningitis with presumed septic embolization of the apex leading to marked bony and fibrous apical changes (unlike pattern seen in suppurative labyrinthitis). (H & E, X 15)

blood flow to the inner ear. Spencer[16] reported 42% of his 300 patients with symptoms or findings of inner ear disease had clearly defined hyperlipoproteinemia.

As a possible contributing mechanism of atherosclerosis in deafness, Penner[17] has speculated that breakdown of sclerotic plaques, and agglutination of erythrocytes and platelets may contribute to deafness associated with age, hyperlipidemia or diabetes mellitus.

The possible reversing effects on hearing loss of a low-cholesterol diet after a person develops hearing loss associated with high blood cholesterol levels, was studied by Rosen and his associates.[13,14] They reported that a change of diet from a cholesterol-rich diet to a low-cholesterol diet actually improved 4 kHz hearing in humans after four years. The difference between those two groups was approximately 10 dB.

METHODS AND MATERIALS

Animal. Rabbits were chosen because of the following: 1) suitability for adapting to high cholesterol diets and then suitability as a hypertension model; 2) ease in measuring the blood pressure; 3) ease in determining hearing thresholds using evoked response and CM; and, 4) in addition to cholesterol levels in the serum, other biochemical parameters including glucose, triglycerides, urea, uric acid, etc, were easy to be analyzed because a reasonable amount of blood could be drawn.

Renal Hypertension. Modified Page type hypertension[18,19] was induced by the following method: Latex rubber capsules for the rabbit's kidneys were made in a manner similar to that described by Abrams and Sobin.[20] Rabbits, weighing approximately 1.3 kg were anesthetized with pentobarbital sodium into the ear vein, the hair over the lumbar region was removed and the skin sterilized with 95% alcohol. An incision along the dorsal and inferior costal margin was made, and the dorsal muscles were split by blunt dissection close to the vertebral column. Thus, a kidney with fatty tissues and adrenal glands was more easily accessible through the extraperitoneal approach. The capsule of the kidney was nicked and peeled off toward the hilus with tissue forceps. The decapsulated kidney was then scooped out and held with the fingers, the widely expanded rubber capsule was placed around the kidney by means of specially designed forceps. The rubber capsule enclosed the kidney snugly but not tightly. The loose neck of the capsule did not compress the renal vessels or ureter. The wound was stitched in the usual manner, and antibiotic powder (Neosporin®) was puffed on the wound for a few days.

Hypercholesterolemia. Hypercholesterol rabbits were induced as follows: rabbits were fed 1000 mg of cholesterol daily. Cholesterol (Merck Co.) was dissolved in peanut oil, and was mixed with 80 gm of rabbit pellets. After the cholesterol food was completely eaten by the animals, an additional 70 gm of the rabbit food without cholesterol and oil was given, therefore, the total amount of rabbit food was less than 150 gm/day. Water was supplied freely from a water bottle. About three weeks later, blood cholesterol levels were between 500 and 1500 mg/deciliter (original levels 45 ± 11 mg/dl) and it gradually rose to 2500 mg/dl within three months.

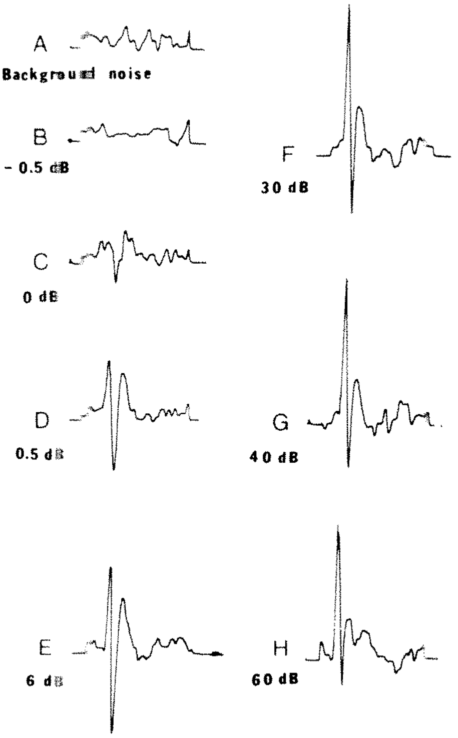

Fig. 3. Auditory evoked responses from the inferior colliculus of rabbit 5, tone pips 10 kHz, 50 msec, repetition 1/sec, 100 sweeps. A - background noise; B - 0.5 dB below threshold; C - threshold; D - only 0.5 dB above threshold gave a clear response; E-H - sound level was increased to 6, 30, 40 and 60 dB above threshold.

Monitoring Blood Pressure. Following the method developed by Morizono et al,[21] the animal's blood pressure was measured with a version of the conventional sphygmomanometer, the "cuff" being a flat inflatable balloon designed to occlude blood flow through the main artery in the rabbit's ear. The flow of blood was detected as changes in the resistance between two electrodes inserted on either side of the artery measured by conventional impedance plethysmography.

Auditory Thresholds. Auditory evoked responses from the contralateral inferior colliculus were used to determine auditory thresholds in the rabbits in the manner described by Aitkin et al.[22]

Bipolar Teflon®-covered stainless steel elec-

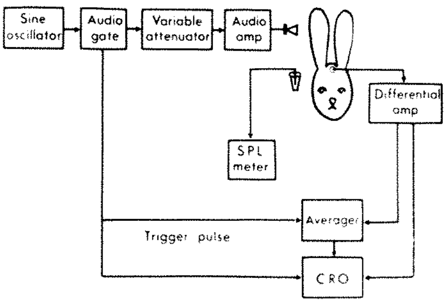

Fig. 4. Schematic arrangements of the equipment used in the study. CRO - Cathode ray oscilloscope.

trodes were prepared by twisting two straws of the wire and cutting the end obliquely.

A bipolar electrode was advanced through the hole in the cranium and located in the inferior colliculus using a micromanipulator and approximate stereotaxic coordinates given by Fifkova and Marsala.[23] The final location was broadly determined from evoked responses to sound clicks. When an optimum response was obtained, the electrode was fixed in place with dental cement and an electrical connector fitted and encapsulated between the supporting screw with the cement.

Subsequent evoked responses to clicks and tones often varied, but after one week stabilized, and the animals gave reasonably consistent audiograms for pure tones over the control period. Figure 3 shows how the responses to tone pips averaged over 100 times provided a very decisive measure of the threshold of hearing, typically within a range of about 1 to 3 dB input sound pressure level. In the rabbit illustrated in Figure 3, only 0.5 dB difference in the input sound (100 times average, tone pip of 10 kHz, 50 msec in duration rise time and fall time 3 msec, repetition 1/sec) gave a clear difference in the average response. The threshold was −9.0 dB SPL at 10 kHz. (S/N ratio 2 when averaged 100 times, was taken as the threshold.)

Sound System. Sound was delivered free field to the left ear canal of each animal. The ear was supported from above and prevented from closing by the insertion of a small funnel. The sound pressure level was measured by using a 1.25 cm B & K Type 4133 condenser microphone from within this funnel as close as possible to the tympanic membrane of the animal. The sound pressure level was recorded from a B & K Type 2604 measuring amplifier.

The tone pips were supplied from a single oscillator via an audio gate. The output of the gate was amplified and supplied to a Geloso horn driver which provided the free field sound. For most frequencies, it was impossible to directly measure the sound input at the threshold level, so an input attenuator was used to first set the sound level above ambient noise level for a reliable SPL reading and attenuation switched in at the input. It was not unusual for rabbits to respond to midrange frequencies at −5 and −10 dB SPL with the animal located in a sound-proof box.

Figure 4 shows a schematic arrangement of the apparatus in relation to the animal.

Controls. All animals were tested as controls for periods ranging from two weeks to four months. In other words, each animal served as its own control and subsequent changes in response by hypertension or hypercholesterol trials were analyzed statistically, based on the means and variations during the control period.

The changes in the response, the changes in the systolic blood pressure, and the significance of the level of these changes have been studied. Five percent significant level in *t*-test was used as a significant change (either improvement or deterioration) in the threshold audiogram.

RESULTS

Altogether, 36 rabbits were used in this study of which 24 were used in order to explore the feasibility of producing hypertension and to study the effects of renal encapsulation on the blood pressure, plasma, and on the general health of the rabbits. None of the 24 rabbits were tested for auditory function.

Among the remaining 12 rabbits with implanted electrodes in the inferior colliulus, only 5 rabbits gave a stable and reliable audiogram. The rest showed a gradual or sudden diminution in the audiogram measured by using the sound-evoked responses. The auditory responses reported here were limited to those five rabbits. Of those five rabbits, two (Nos. 1 and 2) were subjected to hypertension trials; two (Nos. 3 and 4) were subjected to a high cholesterol trial, and one (No. 5) was subjected to both hypertension and high cholesterol trials.

Preliminary Study for Renal Encapsulation ($N = 24$). To study the effects of renal encapsulation on the general health of the rabbits, 24 rabbits of similar body weights (1.28 ± 0.2 kg) were used, of which 17 had bilateral renal encapsulation and 7 had sham operations. For the first three weeks following the operation, the increase in the

TABLE 1. RESULTS OF BIOCHEMICAL ANALYSIS OF PLASMA IN NORMAL AND HYPERTENSIVE RABBITS.

		Na^+ mmol/l	K^+ mmol/l	HCO^-_3 mmol/l	Urea mg/ 100 ml	Cholest. mg/ 100 ml	Triglyc. mg/ 100 ml	B. P. mm Hg
Renal Encap. (N=17)	Means	139.0	3.93	24.1	54.4	62.9	108.7	117
	SD	2.6	0.33	3.6	10.6	15.4	51.8	23
	SE	0.6	0.08	0.9	2.6	3.7	12.6	6
Control (N=6)	Means	137.2	4.05	19.8	40.2	48.0	107.3	81.2
	SD	1.8	0.28	2.1	7.1	11.3	51.4	11.1
	SE	0.8	0.11	0.9	2.8	4.6	21.0	4.5

Blood samples taken eight weeks, and blood pressure measured six months following renal encapsulation.

body weight was restricted in the renal encapsulation group, but the gain in the body weight was more marked in this group compared with the control group, and the body weights had reached the same level by six months following the operation.

Biochemical analyses of the plasma in the control and hypertensive groups were done at eight weeks and six months following the operation. The results at eight weeks are shown in Table 1. Among the parameters such as Na^+, K^+, HCO^-_3, urea, cholesterol, and triglycerides, triglycerides varied the most in both groups, but the differences were not significant. Cholesterol values also varied from animal to animal, but the hypertensive group showed higher values (63 ± 15 mg/100 ml) compared with the control group (48 ± 11 mg/ml). At six months, however, all biochemical analysis, including triglycerides and cholesterol, did not differ between the hypertensive group (N=17) and the control group (N=6).

The blood pressure at two weeks was not studied. The blood pressure at six months following the operation in the hypertensive group and in the control group was 117 ± 23 mm Hg and 81 ± 11 mm Hg respectively. Out of 17 rabbits, 11 showed significantly high ($P<0.05$) blood pressure and 7 showed highly significant ($P<0.01$) hypertension, more than 125 mm Hg. It was interesting to note that 9 of the 17 rabbits followed up remained hypertensive one year after the operation (113 ± 10, compared to 80 ± 12 in the remaining 3 control animals).

In Table 2, the number of animals which showed significant changes in blood pressure, urea and cholesterol, and these values corresponding to P-value indicated in the left-most column are shown in parentheses.

Hypertension and Hearing. Both rabbits 1 and 2 showed significantly high blood pressure (Table 3). It was interesting to note that these hypertensive rabbits without cholesterol food also developed hypercholesterolemia. One of the hypertensive rabbits (No. 2) showed high urea, indicating temporary renal impairment. Na^+ also showed a temporary increase. Changes in auditory threshold of rabbits 1 and 2 are shown

TABLE 2. NUMBER OF ANIMALS WHICH SHOWED SIGNIFICANT CHANGES FOLLOWING RENAL ENCAPSULATION

	Hypertension	*Increased Urea*	*Increased Choles.*
P .2	15/17 (97)	4/17 (50)	7/17 (65)
P .1	12/17 (103)	2/17 (54)	5/17 (71)
P .05	11/17 (109)	2/17 (58)	2/17 (77)
P .02	7/17 (118)	2/17 (64)	2/17 (86)
P .01	7/17 (125)	0/17 (69)	0/17 (93)

TABLE 3. ANALYSIS OF PLASMA AND BLOOD PRESSURE OF RABBITS WHICH HAD SUCCESSFUL THRESHOLD AUDIOGRAMS

		B. P. (mm Hg)	*Cholest. mg/ 100 ml*	*Trigly. mg/ 100 ml*	*Urea mg/ 100 ml*	K^+ *mmol/l*	Na^+ *mmol/l*	HCO^- $mmol^3/l$
Control	Mean	81	23	124	44	5	137	18
N=6	± SD	11	13	37	9	1	2	3
First sample								
1 Normal Diet		132**	58*	52	44	3.9	143*	22
2 Normal Diet		123*	352**	56	92**	4.1	144*	22
3 Cholest.-rich		79	1500**	268*	31	4.1	137	24
4 Cholest.-rich		105	1630**	48	33	4.3	142*	20
5 Cholest.-rich		156**	2560**	184*	54	3.4	142*	25
Second sample								
1 Normal Diet		105	32	92	39	3.6	137	16
2 Normal Diet		102	30	62	54	3.9	138	24
3 Cholest.-rich		77	20	28	32	3.8	137	23
4 Cholest.-rich		85	40	30	39	3.8	136	22

Renal encapsulation (hypertensive procedure) was done with rabbits 1, 2 and 5. A diet rich in cholesterol was given to rabbits 2, 4, and 5 for three months, followed by a normal diet for 6 months. Blood samples were taken twice, once at 2 months while on a cholesterol-rich diet (upper column) and at 6 months while on a normal diet following a cholesterol-rich diet for 3 months (lower column).

*5% level; **1% level in the significance. Control = Normal diet.

in Figure 5. Statistically significant changes ($P<5\%$) occurred in both higher and lower frequency ranges without any significant changes in the middle frequency ranges.

In the No. 1 rabbit, the earliest change was the increased threshold at 10 kHz, ten days following renal encapsulation when BP changed from 82 to 102, followed by increased threshold at 8 kHz and 12 kHz. When the changes in the threshold were averaged between 10 and 24 days, the changes in 10 kHz were greatest in the higher frequency ranges, amounting to 12 dB, but this change was not statistically significant.

One remarkable finding in this rabbit was that the auditory function in the lower frequency appeared to improve considerably, and a 25 dB improvement in the threshold was noted at 500 Hz, 19 days following renal encapsulation. The improvement in the lower frequency ranges continued and reached such a level that the difference became significant at two and three months later. Increased threshold at 16 kHz became significant at two months, but insignificant at three months.

Exactly the same phenomenon was noted in rabbit 2, namely, there was an increase in the threshold at higher frequency ranges as well as a decrease in the threshold in the lower frequency ranges amounting to 15 dB improvement at 1 kHz, one week following the hypertensive procedure when the BP became 90 to 100 mm Hg. At two weeks, the response in the higher frequencies deteriorated 13 dB at 10 kHz and 14 dB at 12 kHz, but those changes were not significant when treated statistically.

The dip was noted in both rabbits at 10 kHz, maximum changes on one particular day amounted to 19 dB ($P<5\%$) in No. 1, and 15 dB ($P<5\%$) in No. 2, but the daily fluctuation of the threshold of this frequency made the average change in this frequency during a period of time insignificant.

In summary, from the hypertensive rabbits, there was a decreased threshold response (improvement in hearing) at lower frequency ranges as well as deterioration in the response for the higher frequencies.

Histological study of the temporal bone was not done in this preliminary study. Histopathological studies re-

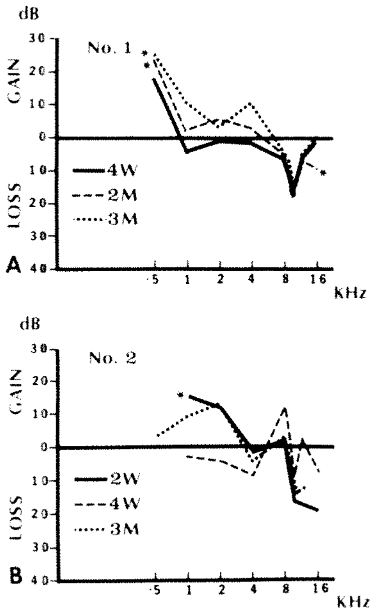

Fig. 5. Changes in auditory evoked responses from hypertensive rabbits, A) No. 1 rabbit; B) No. 2 rabbit. Significant changes ($P < 5\%$) occurred in both higher and lower frequency ranges. A dip was observed at 10 kHz.

ported here were limited to those of the aorta, coronary artery and myocardium. Rabbit 1 was sacrificed 14 months after implantation to the midbrain and nearly 11 months following renal encapsulation. No pathological changes were noted in any of the tissues studied.

High Cholesterol Diet and Hearing. The cholesterol was fed to rabbits 3 and 4 for three months and then the normal diet was resumed. At eight weeks, both showed extremely high cholesterol values (1500 and 1630 mg/dl). Triglycerides were high in rabbit No. 3 (268 mg/dl, $P < .02$). No. 4 rabbit developed a mild hypertension ($.05 < P < .01$). It was very surprising to see that the high cholesterol level in both animals returned to quite a normal level during this six month interval. All other biochemical data became normal as well (Table 3).

Changes in the evoked response threshold from cholesterol-fed rabbits 3 and 4 are illustrated in Figure 6. Both showed a marked decline of the response in the higher frequency ranges. In No. 3 rabbit, as early as two weeks following the commencement of the cholesterol diet, increase in the response threshold (hearing loss) at higher frequencies started with a dip at 10 kHz and 12 kHz.

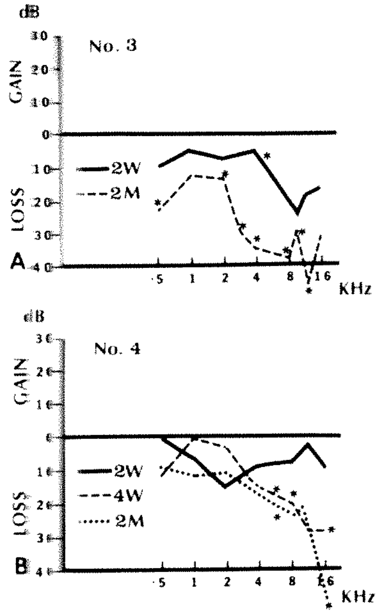

Fig. 6. Cholesterol-fed rabbits A) No. 3; B) No. 4 showed a marked decline in the higher frequency ranges.

The maximum changes observed during this period were 21 dB and 22 dB, but the average change was 15 dB and 17 dB owing to some daily fluctuation in these frequency ranges and thus, statistical analyses for these frequencies were not significant. Two months later, changes in the higher frequency ranges became more pronounced, showing more than 40 dB deterioration at 12 kHz.

No. 4 also showed similar change, steep deterioration in the response at high frequencies at four and eight weeks. As early as two weeks following a cholesterol diet, both animals showed a dip at 10 kHz (No. 3) and at 2 kHz (No. 4) respectively. A small recovery (no more than the original level) occurred at 2 kHz dip. Both No. 3 and No. 4 rabbits were sacrificed six months

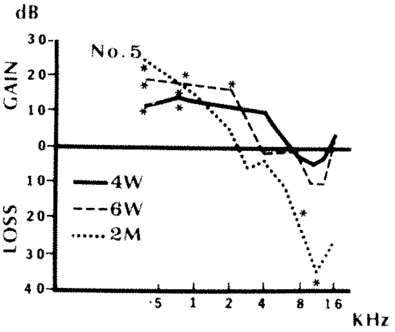

Fig. 7. Combination of both hypertension and cholesterol diet caused improved auditory function at lower frequency ranges together with a deteriorated auditory function at higher frequencies.

after the cessation of the cholesterol food. Both had gross atheromatous changes in the aorta as well as in the coronary artery. No. 3 had occluded vessels in the myocardium but No. 4 had more severe changes such as partial degeneration of the myocardium and "foam cells" between the muscle fibers. The reason for the more severe changes in No. 4 could be explained partly by the fact that 1) the blood pressure was much higher in this rabbit, and 2) there was a higher cholesterol level in the blood.

Combination of Hypertension and Cholesterol Diet. Only one rabbit (No. 5) was subjected to this experiment. The highest values in the cholesterol (2560 mg/dl) as well as in the blood pressure (156 mm Hg, $P<.01$) were noted. The threshold audiogram from this animal is illustrated in Figure 6. It was interesting to note that improved hearing response was noted at lower frequency ranges together with a slight dip at higher frequencies which started as early as two weeks following renal encapsulation. Four weeks later, the improvement in 500 and 1000 Hz became significant. The cholesterol diet was commenced one month after renal encapsulation when the blood pressure reading rose to 112 from 77 mm Hg. Blood pressure kept rising and reached 165 mm Hg two months following cholesterol diet and the rabbit died one month later.

Two weeks following cholesterol diet, gradual deterioration in the response at higher frequencies began, and four weeks following cholesterol (eight weeks following renal encapsulation), the response at higher frequencies deteriorated markedly with a dip at 12 kHz. It was noted that the response at the lowest frequency (500 Hz) improved still, making a total of 22 dB ($P<5\%$) together with deterioration of the response at 12 kHz 23 dB ($P<5\%$) from the control level.

DISCUSSION

The method of using latex rubber capsules was found to be a very satisfactory method for producing hypertension in the rabbit. The maximum hypertension was obtained about two months following the procedure, then it reduced gradually but did not return to the control level and retained a moderate hypertension.

In our hypercholesterol experiments, there was a time interval between the last measurement of the evoked response and the preparation of histological material from the rabbits used, hence, exact stages of the atheromatous changes of these vascular systems at the time when the audiograms were made were not known. However, rabbits 3 and 4 which were sacrificed nine months after the commencement of the cholesterol diet had shown an obvious change in the aorta and coronary arteries. Changes in the response (decrease) became apparent only two weeks after such a diet began. Although it is difficult to tell whether actual blood flow to the cochlea had already decreased at that time or some other metabolic imbalances were also involved, all three rabbits which were on a cholesterol diet showed a steady deterioration of the response in higher frequencies to the same degree; this seemed to be sufficient evidence to state that the cholesterol diet induced the response change. When the cholesterol and hypertension were combined, both the phenomena following the hypertension (improved auditory function in the lower frequencies and a dip and a mild loss in the auditory function at higher frequencies) and the phenomenon accompanying cholesterol (steep loss for high frequency auditory responses) appeared on the audiogram. The degree of response deterioration at high frequency ranges did not differ from those on a cholesterol diet only.

In the current experiment, evoked responses from the inferior colliculus are interpreted as an indication of hearing. The best frequency of hearing (i.e., smallest sound pressure required to elicit detectable evoked response) was around 8 kHz and the mean of the tuning curve for those successful rabbits was almost identical to those reported by Aitkin et al[22] with the envelope of the tuning curves for single unit responses from the inferior colliculus in rabbits.

This preliminary study was concerned with the potential clinical effect of hypercholesterolemia and hypertension on hearing. Our preliminary study revealed that hypertension alone caused a dip at high frequency ranges, but did not cause progressive deterioration of auditory function. We could not explain why those animals which were subjected to hypertension showed improved auditory function for lower frequency ranges. Similar phenomena, however, have been observed by many workers, e.g., Kawata,[24] Luz et al,[25] and Kiang et al,[26] as a result of noise induced deafness.

A clinical study of Drettner et al[27] could not demonstrate any relationship between cardiovascular risk factors and the amount of hearing loss on 1000 people at the age of 50. However, Cunningham and Goetzinger[28] found that extrahigh frequency (10-18 kHz) hearing loss occurred in 20 hyperlipidemic subjects aged between 20 and 50, who had no history of noise exposure. Longitudinal prospective studies are necessary. The possible clinical relevancy between hypercholesterolemia and high tone deafness, so called "aging deafness," is obvious. The cholesterol value in the rabbits' plasma rose at first, but became normal several months following cessation of cholesterol food. Obvious atheromatous changes of the vascular system with normalized cholesterol levels in the animal indicate the practical importance of frequent measurements of blood cholesterol levels in order to recognize any possible hyperlipoproteinemia, with associated atheromatous changes of the system, which has been suggested as one of the causative factors of sensorineural deafness in man.

A single measurement of blood cholesterol levels does not correlate with atheromatous changes in the vascular system and this must explain the result of Drettner et al,[27] who did not find any correlation betwen hearing loss and cardiac risk factors.

There is ample evidence to indicate that hypertension alone does not cause progressive auditory dysfunction. Hypertension accelerates the atherosclerotic process and the atherosclerosis seems to play an important role in causing auditory dysfunction.

The animal model developed in this preliminary study has proven to be a useful tool in studying the relationship between cardiac risk factors (hypertension and serum cholesterol level) and auditory function. Of 12 animals implanted, 5 were successful. There is a need to expand and repeat these experiments before establishing conclusions. Important questions relating to whether or not cholesterol directly or indirectly influences the cochlea; or whether the auditory function of the rabbit once subjected to the cholesterol-rich diet can be reversed, also requires further study. Also, since no pathological corollary studies were done in this preliminary study, this will be done as well.

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IV INTERNATIONAL SYMPOSIUM ON ACOUSTIC IMPEDANCE MEASUREMENTS

The IV International Symposium on Acoustic Impedance Measurements will be held September 26-28, 1979 in Lisbon, Portugal. For further information write: Organizing Secretariat, Clinica Fono-Audiologica, Rua Conde Redondo, 119-3°-Lisboa, Portugal.

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ASYMMETRY OF THE INTERNAL AUDITORY CANALS WITHOUT ACOUSTIC NEUROMA

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During the past five years, nine patients with "significant" unilateral enlargement of one internal auditory canal by polytomography were subsequently found to have freely filling canals on contrast posterior fossa myelography. The radiographic appearance of the enlarged canals varied greatly and included all the various configurations usually suggestive of acoustic neuroma. Likewise, the clinical presentation varied greatly from asymptomatic to highly suggestive of cerebellopontine angle tumor. This series underscores the essential nature of posterior fossa studies in the evaluation of potential acoustic neuromas and the variability of the normal architecture of the internal auditory meatus.

Naughton and Petasnick have described six patients with symptomatic acoustic neuroma which produced no change in the porus acusticus or internal auditory canal, but which were evident on contrast cerebellopontine cisternography.[1] The majority of acoustic neuromas should affect the size or shape of the internal canal and porus.

In reviewing the tomographic findings in 89 cerebellopontine angle tumors, Valvassori found 78% were positive for the presence of a tumor.[2] He further found that iophendylate contrast examination of the cerebellopontine cistern demonstrated all of the tumors in his series. In another study, Valvassori found four instances of false positive tomographic studies in suspected acoustic neuromas, an incidence less than 2%.[3]

We have found only two reports of significant unilateral enlargement of the internal auditory canal without acoustic neuroma. Fraser and Carter found an enlarged internal auditory canal in a patient who was being treated for an arteriovenous malformation.[4] Audiometric and caloric tests were normal. Iophendylate cerebellopontine cistern study revealed filling of both internal canals to the lamina cribrosa.

Hill et al reported a patient with neurofibromatosis and a seven year history of progressive left-sided hearing loss.[5] On tomograms, the right porus was 8 mm in height while the left was 10 mm. On contrast cerebellopontine angle cisternography, no mass was found on either side. Sarwar and Swischuk report another patient with neurofibromatosis and bilaterally enlarged internal canals, but no hearing disturbance, in whom oil filled both internal canals and no mass was present.[6]

We have reviewed our case material and have found nine patients in whom significant asymmetry of the internal canals or porus acusticus was present, but in whom no abnormality was found on iophendylate cisternography. Three patients had no hearing disturbance on audiometric examination. In one patient, an internal auditory canal abnormality was discovered during neurological examination for unrelated complaints. The other two were being evaluated for positional vertigo.

METHODS AND MATERIALS

The criteria used for determining abnormali-

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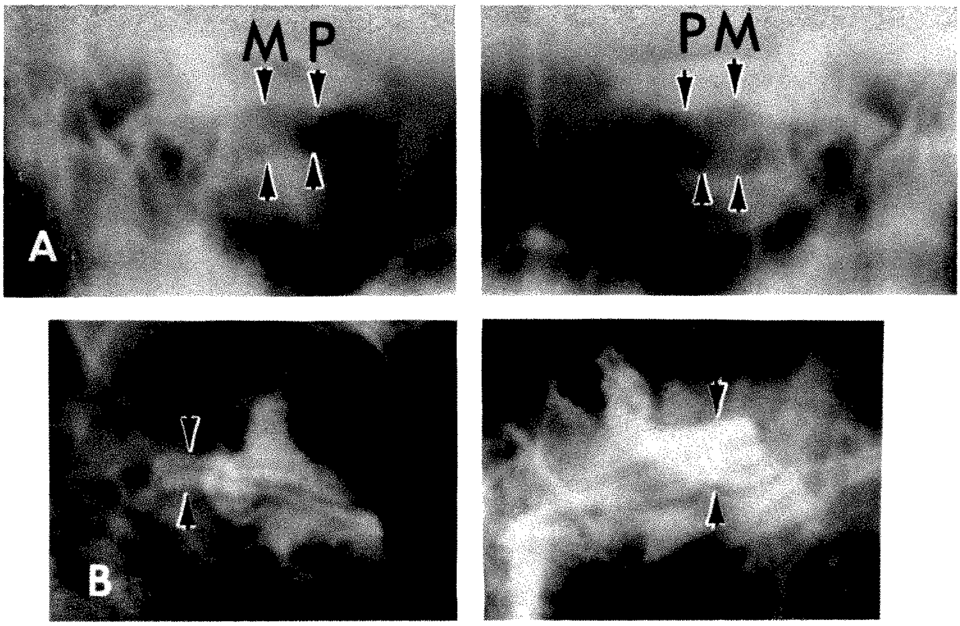

Fig. 1. Generalized increase in internal canal size in Case One. A) Coronal tomograms show the left porus (P - arrows) and mid canal (M - arrows) to be more than 2 mm larger than the right. B) Frontal oil study showing diffuse canal asymmetry (arrows) without a mass.

ty of the asymmetrical canals in this study are those reported by Valvassori[2,3,7-9] and Lapayowker and Cliff.[10] These changes include: 1) internal auditory canal widening of more than 2 mm; 2) shortening of the posterior canal wall by at least 3 mm in comparison to the opposite side; and 3) change in the position of the crista falciformis.

CASE REPORTS

Case 1. This is a 31-year-old male with a chief complaint of left hypacusis without tinnitus or vertigo. Audiometric examination showed a pure tone average (PTA) of 78 dB in the left ear (AS) and 12 dB in the right ear (AD). Speech discrimination (SDS) was 0% AS and 100% AD. A Type 4 Békésy audiogram was elicited. Electronystagmography (ENG) revealed brisk symmetrical responses with no positional or latent nystagmus.

Tomographic temporal bone examination revealed generalized height increase of the left internal auditory canal. The porus and midcanal on the left was 2 mm larger than the right, with more than 2 mm shortening of the posterior wall (Fig. 1A).

Cerebellopontine angle cisternography (CPAC) confirmed the enlarged left canal. Oil filled both canals to the lamina cribrosa (Fig. 1B).

No symptomatic progression has occurred during an eight-year follow-up.

Case 2. This is a 14-year-old male whose internal auditory canal asymmetry was discovered on skull filming during workup for a behavioral disorder. No symptoms were referable to the ears. Auditory system testing was normal but right beating spontaneous nystagmus was found on ENG. No canal paresis was present.

The left internal canal height was 3 mm larger than the right both at the porus and midcanal. The left posterior wall was 2 mm shorter than the right. The crista falciformis was 2 mm above the floor on the right and 4 mm above the floor on the left. The oil study confirmed asymmetry and both canals filled well.

The patient continues to be asymptomatic two years after this examination.

Case 3. This is a 50-year-old male complaining of gradual right hypacusis not associated with tinnitus or vertigo. PTA was 12 dB AS and 54 dB AD. SDS was 96% AS and 50% AD. ENG showed brisk symmetric responses with no positional or latent nystagmus.

Tomographic study revealed symmetrical canals in the frontal study. Basal views showed enlargement of the right porus acusticus 5 mm greater than the left. Oil study confirmed the asymmetry and both canals filled completely.

No change has occurred during five years of follow-up.

Case 4. This 47-year-old, morbidly obese female presented to general surgery for a gastric bypass procedure. She incidentally related a six-month history of positional vertigo without tinnitus or hypacusis. Audiometric examination revealed an SRT of 5 dB aures unitas (AU). SDS was 100% AU and there was no tone or acoustic reflex decay. ENG was normal.

Tomograms revealed enlargement of the right porus on basal views as in Case 3. The right porus was 12 mm, the left 8 mm in size. No mass was present on oil study.

Six months later the patient's vertigo was unchanged.

Case 5. This is a 56-year-old male with retinitis pigmentosa, spinocerebellar degeneration and bilateral hypacusis (Usher's syndrome). Audiometric examination revealed a severe mixed loss bilaterally, producing a masking dilemma. Discrimination could not be demonstrated to be better than 32% in either ear. ENG revealed a distinct canal paresis AD.

On tomographic examination, the midportion of the left canal was 3 mm greater than the right. Other dimensions were symmetrical. Oil study confirmed the left midcanal enlargement but both canals filled completely.

His basic disease continued to progress during a three-year follow-up but no audiologic changes occurred.

Case 6. This 56-year-old female presented with gradual right hypacusis, tinnitus and "unsteadiness" but this was not associated with true vertigo. PTA was 25 dB AS and 55 dB AD. SDS was 88% AS and 32% AD. Significant right-sided tone decay was demonstrated. ENG showed a canal paresis AD. Brain stem evoked response audiometry and neuroma specific circulating serum antibodies both suggested an acoustic neuroma.

Her right porus and midportion measurements were 3 mm greater than the left but the posterior canal length was symmetrical. Oil study confirmed this asymmetry and both canals filled completely.

Case 7. This 43-year-old male complained of light-headedness while exercising during the past year. He had stable right-sided hypacusis and tinnitus resulting from mumps at age 29. Audiometric examination showed PTA of 85 dB AD and 10 dB AS. SDS was 65% AD and 100% AS. There was recruitment but no tone decay AD. ENG showed brisk symmetric caloric responses without positional or latent nystagmus.

Radiographic examination showed right porus and midcanal diameters slightly more than 2 mm greater than the left. The posterior walls were equal in size. Oil study revealed complete filling bilaterally.

Case 8. This 55-year-old male presented with a six-month history of true vertigo when straining, looking up, or looking to the left; this was unassociated with tinnitus or hypacusis. His hypertension was controlled by Dyazide®. He also took nicotinic acid. Audiometric examination demonstrated a symmetric high frequency loss AU with PTA 5 dB AU and SDS of 88% AD and 100% AS. High frequency SISI was positive and the alternate binaural loudness balance test (ABLB) showed recruitment. There was no tone or acoustic reflex decay. ENG showed mild canal paresis AS.

Tomograms revealed a left porus 2 mm larger than the right. Midcanal and posterior wall diameters were nearly equal. A pseudofunneling effect was present medial to the left porus without thinning of the canal roof. Canal size asymmetry was present on the lateral views. An oil study was only done on the left. The canal filled completely.

Case 9. This 33-year-old male presented with a three-year history of episodic vertigo associated with nausea but not associated with tinnitus, hypacusis or aural fullness. Audiometric examination revealed PTA of 10 dB AU with SDS of 100% AU. There was no tone decay present AU. ENG showed a distinct canal paresis AD.

Tomography revealed enlargement of both the porus and midcanal on the right. Each measured 3 mm greater than the left. The posterior wall was nearly symmetrical. Complete canal filling with oil occurred bilaterally.

Valium® has suppressed his symptoms over a two-year period.

Radiographic findings are summarized in Table 1.

DISCUSSION

The clinical and audiological findings in our study group represent an entire spectrum from asymptomatic to highly suspicious of acoustic neuroma. Three cases had normal audiological findings and two of these had either normal or minimal ENG findings. Of the six cases with hypacusis, three had an SDS of 50% or below and four had a significant canal paresis on caloric testing of the appropriate ear. Two of the patients with unilateral hypacusis proved to have significant pure tone and/or acoustic reflex decay, considered to be good evidence of a retrocochlear lesion. Two others had marked recruitment suggestive of cochlear damage with no tone decay. One patient (Case 6) had significantly increased latency on brain stem evoked response audiometry and neuroma specific circulating serum antibodies.

Such diversity is entirely consistent with a group of patients with surgically proven acoustic neuromas.[11,12] There was nothing in the clinical and audio-

TABLE 1. RADIOGRAPHIC FINDINGS IN NINE PATIENTS WITH INTERNAL AUDITORY CANALS (CORRECTED FOR MAGNIFICATION)

Case		*Right*	*Left*
1	Porus	5 mm	7 mm
	Midcanal	6 mm	8 mm
	Length	10 mm	8 mm
2	Porus	5 mm	8 mm
	Midcanal	6 mm	8 mm
	Length	11 mm	9 mm
	Porus (lat. view)	small	large
	Crista	2/4 mm	2/6 mm
3	Porus A-P (Basal view)	12 mm	7 mm
	Other diameters equal		
4	Porus A-P (Basal view)	12 mm	8 mm
	Other diameters equal		
5	Porus	7 mm	7 mm
	Midcanal	7 mm	10 mm
	Length	9 mm	8 mm
6	Porus	7 mm	4 mm
	Midcanal	7 mm	6 mm
	Length	11 mm	11 mm
7	Porus	7 mm	5 mm
	Midcanal	7 mm	5 mm
	Length	9 mm	10 mm
8	Porus	6 mm	8 mm
	Midcanal	6 mm	7 mm
	Length	9 mm	10 mm
	Porus (lat. view)		P.F.
	Crista	Not asym.	
9	Porus	8 mm	5 mm
	Midcanal	8 mm	5 mm
	Length	11 mm	10 mm
		P.F.	

P.F. - Pseudofunneling.

logical findings in this group which was useful in predicting the likelihood of a false positive tomographic study prior to the definitive posterior fossa contrast study.

Similar diversity was present in regard to the radiographic findings. Four general patterns of enlargement were present. One patient (Case 5) had only midcanal enlargement. Two (Cases 6 and 7) had an enlarged porus and midcanal with equal posterior wall lengths. These changes suggested primarily an intracanalicular lesion. A tumor producing such change would be less than 2 cm in size. Such tumors are best evaluated primarily by the definitive iophendylate contrast study.

Larger lesions were suggested by findings in two patients (Cases 8 and 9) who had diffuse canal enlargement with "pseudofunneling," and by two patients (Cases 1 and 2) with diffuse enlargement accompanied by shortening of the posterior wall. A lesion principally within the cerebellopontine cistern was suggested by tomographic findings in patients three and four.

Larger acoustic neuromas in the cerebellopontine angle cistern have recently been studied by the newer technique of computerized axial tomography (CAT) augmented by intravenous iodinated contrast material infusion. However, as Davis et al point out, the acoustic neuroma must be larger than 2 cm in size before it can be reliably demonstrated with a CAT scan.[13] While CAT scanning was not available to us at the time these patients were being evaluated, Cases 1-4, 8 and 9 might have been positive had tumors been present.

Robbins et al have illustrated that enlargement of the internal auditory canal may be demonstrated in connection with acoustic neuromas which cannot otherwise be demonstrated by the CAT scan even with iodine infusion.[14] Iophendylate studies should be done on such patients to confirm the presence of a mass and ascertain its size in order to choose the proper surgical approach.

There has been diversity of opinion regarding anatomic variations in size of the internal auditory canal. Table 2 illustrates the studies of Camp and Cilley,[15] Papangelou[16] and Valvassori.[7] Camp and Cilley found porus and midportion size variations up to 3 mm in vertical height while Valvassori found no greater than 2 mm variations in his

TABLE 2. COMPILATION OF BILATERAL SIZE VARIATION OF THE INTERNAL AUDITORY CANAL

Bilateral Variation	*Camp and Cilley*[15]	*Papangelou*[16]	*Valvassori and Pierce*[7]
1. Vertical diameters			
Up to 1 mm	75%	87%	99%
1 to 2 mm	23%	9%	1%
2 to 3 mm	2%	4%	—
2. Posterior wall length			
Up to 1 mm	27%	59%	86%
1 to 2 mm	38%	26%	13%
2 to 3 mm	23%	9%	1%
3 to 4 mm	7%	2%	—
4 to 5 mm	5%	4%	—

series. Posterior wall variations up to 5 mm were found by Camp and Cilley and Papangelou, while Valvassori found no greater than 3 mm variations.

This material would suggest that the standards of canal size variation may be understated by Valvassori. Canal size, however, should never be used alone in the assessment of patients with symptoms and/or audiological signs of acoustic neuroma. We feel that clinical or radiographic plain examinations where suggestive of acoustic neuroma, should lead to further, definitive radiographic contrast examination. Similarly, oil studies help differentiate the size of an acoustic neuroma to allow the surgeon to determine if the translabyrinthine, middle fossa or posterior fossa approach is best.

The differential diagnosis of internal auditory canal asymmetry is extensive. Anatomic variations are represented by this series. Unilateral enlargement in neurofibromatosis has been described by Hill et al.[5] Valvassori has described one child with an inner ear anomaly who also had an enlarged internal auditory canal.[17]

Decrease in size of one internal auditory canal resulting in apparent enlargement of the other canal may also occur. Unilateral involvement by fibrous dysplasia or Paget's disease may result in one small canal. Osteopetrosis is usually symmetrical, but may progress at a different rate on the two sides resulting in asymmetry. A small internal canal was commonly associated with inner ear anomalies (11 cases) in the series of Valvassori et al.[17] The authors have also seen patients with asymmetrical small canals or porus acusticus who have variations in the amount of petrous ridge pneumatization. Ordinarily, oil studies are not needed to recognize the asymmetry produced by diseases or variations resulting in a small internal auditory canal.

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NINCDS NOTES*

NINCDS LAUNCHES PET PROGRAM

A new program to help develop positron emission tomography (PET) for the study of human cerebral metabolism and biochemistry has been launched by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS). Announcements of grant support availability have been sent to institutions and individuals with a possible interest. The deadline for NINCDS to receive applications is December 1 for applications to be reviewed by the NINCDS National Advisory Council in May 1979.

The PET technique entails injection or inhalation of short-lived radioisotopes such as O^{15}, C^{11}, F^{18}, and N^{13} incorporated into compounds like glucose, carbon monoxide, and ammonia. As they decay, the isotopes emit positrons, so that the distribution and metabolic fate of the tagged compounds can be followed with a computerized PET imaging device.

Detailed information about the program and requests for applications should be addressed to: Positron Emission Tomography Program, NINCDS, Room 8A-13, Federal Building, 7550 Wisconsin Avenue, Bethesda, Maryland 20014. Telephone: (301) 496-4226.

TIDA AWARDS APPROVED

Sixteen of 23 Teacher-Investigator Development Award (TIDA) applications recommended for approval by the National Advisory Neurological and Communicative Disorders and Stroke Council during fiscal year 1978 were funded. Two of these funded applications had been carried forward from FY 1977. Two additional approved applications would have been funded but were withdrawn at the candidate's request. With this total of 18 approvals, competing institutions had a 78% chance of obtaining TIDA support for their candidates.

NEW EXTRAMURAL APPOINTMENTS

Several new NINCDS Extramural Program appointments have been made with more changes anticipated.

Dr. John C. Dalton has been named Director of the Extramural Activities Program, a position left vacant by the death of Dr. Kenneth Hisaoka.

Dr. Buckminster Ranney has been appointed Deputy Director of the Communicative Disorders Program (CDP). He will also serve as Acting Director of that Program until Dr. Tower can review and act upon a search committee's recommendations for a replacement for Dr. Wesley H. Bradley, former CDP Director, who left the Institute several months ago.

SURGICAL NEUROLOGY BRANCH

Dr. Paul L. Kornblith has been appointed Chief of the Surgical Neurology Branch, NINCDS. Also joining the staff are Dr. Eugene A. Quindlen and Dr. Barry H. Smith, who will work with Dr. Kornblith to develop programs to investigate fundamental neurosurgical problems. Tissue culture studies of benign and malignant tumors of the nervous system, including pituitary tumors, will be a major part of the new team's efforts. The biological behavior of tumor cells will be studied, as well as their ultrastructural, electrophysiological, biochemical and immunological characteristics.

The investigators also will study nerve regeneration in the hope of finding ways to promote recovery of lost nerve, brain, and spinal cord function.

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*This column is prepared monthly by the Office of Scientific and Health Reports, National Institute of Neurological and Communicative Disorders and Stroke. For further information write or call Carolyn Holstein, NINCDS/OSHR, NIH Bldg. 31, Room 8A-16, Bethesda, MD 20014. (301) 496-5751.

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TINNITUS: DIAGNOSIS AND TREATMENT

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Few conditions are seen as commonly by the otologist and are more poorly understood than subjective tinnitus. Tinnitus has been reported in as high as 80% of patients seen in an otolaryngology practice. This symptom is especially marked in patients with a hearing problem and can be so severe that it becomes incapacitating. Careful diagnosis and classification of tinnitus is important for understanding of the problem. Identification of the frequency and intensity of masking, using a tinnitus analyzer, is useful in selecting the form of treatment. Analysis of the history, physical findings and the use of special electrocochleography and brain stem evoked response audiometry help to identify the site of lesion, which may be within the cochlea, cochlear nerve, cochlear nucleus, brain stem, midbrain or auditory cortex. Specific disease entities should be identified and treated. Lesions of the end-organ or cochlear nerve can be treated when necessary by translabyrinthine or middle cranial fossa section of the cochlear nerve. Tinnitus from cervical nerve lesions can be treated by rhizotomy. The use of a hearing aid or introduction of a sound with a tinnitus masker has been found to be 82% effective in suppressing tinnitus. Maskers can be combined with a hearing aid in some cases. The pathogenesis of tinnitus is discussed, but the method of action of tinnitus relief by auditory stimulation is still unclear. A thoughtful and complete examination with our new diagnostic tools and the judicious selection of therapy now makes it possible to give relief to the majority of patients suffering with disturbing tinnitus.

Few conditions are more poorly understood and are seen as commonly by the otologist than subjective tinnitus. Tinnitus has been reported in as high as 80% of the patients seen in an otolaryngology practice. This symptom is especially marked in patients with a hearing problem[1,2] and can be so severe that it becomes incapacitating. The development of a tinnitus masker[3-5] has offered relief to a significant number of patients. The purpose of this paper is to review the diagnosis, classification and treatment of patients with subjective tinnitus and to present the authors' results of treatment.

DIAGNOSIS AND CLASSIFICATION

All patients complaining of tinnitus should have a neurootologic examination, including a careful history, physical examination, audiogram for pure tones and speech discrimination, electronystagmogram (ENG) and petrous pyramid x-rays. Tinnitus, which is one of the five cardinal symptoms of ear disease, can mark the onset of almost any otologic disease.[6-8] Tinnitus can be classified as objective or subjective.[9]

Objective tinnitus has also been called dynamic, vibratory, pseudo or extrinsic tinnitus. Objective tinnitus can potentially be heard by an examiner and can be of two general types, mechanical or vascular. Palatal,[10] tensor tympani or stapedial myoclonus, as well as an abnormally patent eustachian tube[11] are detected on physical examination and a specific treatment is indicated for each condition. Of the vascular abnormalities that cause objective tinnitus, arteriovenous fistulas, either extracranial from occipital artery to the transverse sinus or intracranial from the middle meningeal artery to the superior petrosal sinus, or occasionally after trauma from the carotid artery to the cavernous sinus, are in the majority. Venous turbulence from the impingement of the transverse process of the first cervical vertebra or the internal jugular vein,

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can occasionally be heard. The senior author has seen a large hemangioma of the external ear which caused objective tinnitus. It has been suggested that a plaque in the internal carotid artery could cause some otherwise unexplained objective tinnitus. The exact nature of most causes of objective tinnitus can be determined by contrast radiography.

Subjective tinnitus, also called static, nonvibratory, or intrinsic tinnitus is heard only by the patient and involves the neural mechanisms of the ear or auditory pathways. Care must be taken to exclude cerebellopontine angle tumors and brain stem lesions. Both the pathology and the anatomic site of any lesion should be determined. Examinations of value include five-hour glucose tolerance tests, lipid phenotype, visual evoked response testing (VER), electrocochleography (ECochG) and brain electrical response audiometry (BERA).

Subjective Tinnitus – Evaluation. In addition to a careful medical history, answers to a tinnitus questionnaire are obtained. Information desired includes the duration, location, severity, and a description of the quality of the tinnitus. Situations which improve or aggravate the tinnitus are identified. Information regarding smoking, intake of caffeine, head injury, noise exposure, serious illness or ototoxic drug ingestion is obtained. This questionnaire is a modification of those already available.[12]* Characterization of the patient's tinnitus begins with a determination of his air and bone conduction threshold, as well as speech discrimination. Tinnitus matching is performed by presenting pure tones, narrow (one third octave) band or wide band noise over a sweep frequency audiometer. The patient identifies the components of the presented sounds which seem to be identical to his tinnitus or portions of his tinnitus. The intensity of the patient's tinnitus is determined.

By stimulating the ear which has tinnitus with the sounds identified during the tinnitus matching procedure or narrow band of noise, around the identified sounds, a high percentage of patients with tinnitus can be masked. Masking is attempted ipsilaterally and contralaterally. In some patients, a variable width noise band has been helpful in tinnitus matching and masking. For these patients, a tinnitus analyzer has been developed (Fig. 1),** which can be adjusted to a narrow or wide band of noise for matching and masking.

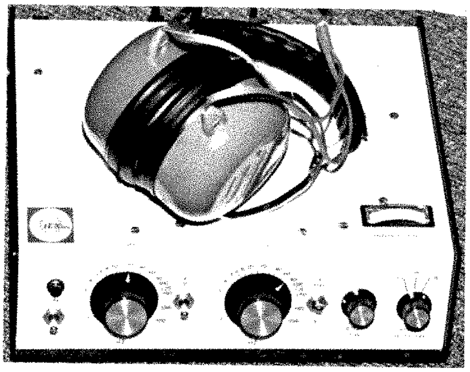

Fig. 1. Tinnitus analyzer.

Tinnitus Display. The frequency and intensity of a patient's tinnitus are marked on the audiogram with a capital "T." If complex tinnitus is found, then the several components or frequencies are marked, or the sound is described in a note. The masking level (narrow or broad band) is represented by a shaded area of which the width indicates the number of combined frequencies necessary to mask the patient's tinnitus and the height indicates the minimum intensity of the masking sound. Cross-hatching can also be used with red hatched lines to show the width of the noise band and the intensity required for masking when the masking is presented to the right ear, and blue or black cross-hatching to demonstrate the width of the noise band and the intensity required for masking when the masking is presented to the left ear. This allows demonstration for all parameters of the patient's tinnitus. A check is made to see if any residual inhibition (or delay of return of tinnitus following exposure to masking sounds) is present.

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*Vernon J: Personal communication.

**Instrumentation and Control Systems, Inc., Addison, IL.

Residual Inhibition. If the patient's tinnitus can be masked, a suitable frequency and intensity of masking sound is presented to the patient for one minute; the tone is stopped and the patient is asked to report when the tinnitus returns. A minimum effective level of sound is used to prevent contamination of results by temporary threshold shift.

TREATMENT

A multifaceted approach to the treatment of tinnitus should be available, depending upon the problem. Treatment of subjective tinnitus may be 1) medical, 2) surgical, 3) hearing aid and/or masker or 4) biofeedback.

MEDICAL

Reduction to an ideal weight, or control of serum cholesterol and triglycerides sometimes will be all that is needed to eliminate a patient's tinnitus. A commonly used medical therapy involves vasodilators such as nicotinic acid[13] and intravenous or intramuscular histamine. The administration of large doses of Vitamin A has been advocated.[14-18] Intravenous Xylocaine® (lidocaine) and oral Tegretol® (carbamazepine) have been used.[19] Identification and treatment of otologic allergy may eliminate tinnitus. The cytotoxic food test is especially useful, since foods are more commonly the cause of ear allergies.

SURGERY

Without considering specific surgical treatments for the relief of an underlying problem such as stapedectomy for otosclerosis or the endolymphatic subarachnoid shunt for Ménière's disease, the surgical treatment of subjective tinnitus primarily involves labyrinthectomy or translabyrinthine VIII nerve section.[20,21] Destruction of the vestibular end-organ by labyrinthectomy has been successful in relieving tinnitus originating within the inner ear. The procedure is ideal for cases with tinnitus in the presence of chronic otitis media and relatively useless hearing and vestibular function. The procedure allows destruction of the end-organ without direct contact with the cerebral spinal fluid; thereby, meningitis can be avoided.

Case 1. A 46-year-old Caucasian female had vertigo, loud right tinnitus, and sensorineural hearing loss following five tympanoplasty procedures on her right ear for chronic otitis media. During one of the previous procedures, the stapes was found to be fixed with tympanosclerosis, was removed, and a cartilage strut was placed from the tympanic membrane to a perichondrial graft overlying the oval window. At the time of her examination by the authors, she complained of persistent disabling instability, episodes of moderate vertigo, with nausea and loud right tinnitus. Hearing for pure tones was at the 90 dB level, with no speech discrimination. The tympanic membrane was intact. ENG showed a 21% reduced vestibular response in the right ear. On the day preceding surgery, an attempt was made to eliminate her tinnitus. With the patient's involved ear turned upward, 0.3 ml 10% cocaine was injected through the tympanic membrane immediately over the round window. Within ten minutes, she developed vertigo, nausea and vomiting, with nystagmus beating towards the injected ear. The symptoms lasted for three hours, but at no time did she have any change in her tinnitus. Under general anesthesia, using a postauricular incision, a complete labyrinthectomy was performed by removing the three bony semicircular canals and the contents of the vestibule. The middle ear was obliterated with bone paste and the labyrinthine and mastoid cavities were filled with bone paste and Proplast®. Two months after surgery, she had regained her stability and, occasionally, now has mild whistling tinnitus which does not disturb her.

COMMENT: This patient demonstrates that disease such as chronic otitis media can involve the inner ear and produce tinnitus in that site. Surgical destruction of that area when hearing is useless will generally alleviate the disabling portion of tinnitus. The surgeon, however, should never promise that the procedure will be successful. An attempt to anesthetize the middle ear or inner ear has been proposed to test[22,23] the possible effectiveness of labyrinthectomy. In this case, even though vestibular anesthesia was accomplished, the tinnitus was unchanged, but good relief after surgery resulted, which suggests that the test is not reliable.

Case 2. A 63-year-old Caucasian female had a moderate degree of right tinnitus following a right facial paralysis that had occurred 18 years before; she had recovered 80% motion with 30% synkinesis. In October 1975, a small neuroma was partially removed from the internal auditory canal on the right by the suboccipital approach. Following this surgery, she developed loud, troublesome tinnitus. Labyrinthectomy was performed through the

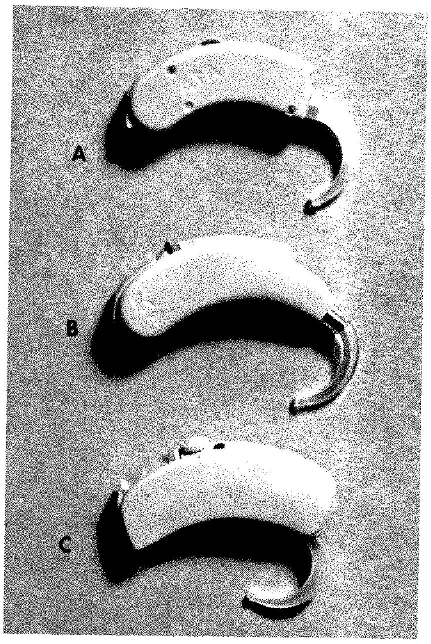

Fig. 2. A) Broad band tinnitus masker, B) High frequency tinnitus masker, C) Combination masker and hearing aid.

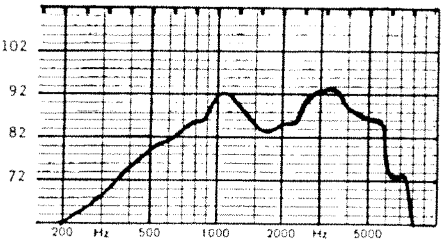

Fig. 3. Wide band tinnitus masker output. Coupler sound pressure level dB. RE: 20μ Pa.

right external auditory canal in July 1976, with no change in her tinnitus. She was first examined by the authors on March 31, 1977 and complained bitterly of tinnitus. She had no caloric or auditory responses in the right ear. Loud sounds heard through her normal ear would disturb her and cause shaking in the body. She had been referred to us for translabyrinthine VIII nerve section. Contralateral administration of masking sounds did not relieve the tinnitus. On April 14, 1977, under general anesthesia, the right internal auditory canal was exposed by the translabyrinthine approach and a 6 x 6 x 6 mm cochlear nerve neuroma was found within the internal auditory canal. The facial, superior vestibular and inferior vestibular nerves passed around this tumor. The tumor was completely removed, demonstrating the proximal and distal cochlear nerve stumps and leaving the facial nerve intact. Immediately upon awakening from surgery, she experienced relief of her tinnitus. Her facial nerve function was unchanged. Her postoperative course was uneventful, and she has remained well and relieved from her severe tinnitus and intolerance to sounds heard by her normal ear. Mild tinnitus remains.

COMMENT: This case illustrates the phenomenon of increased tinnitus in an ear which has no hearing when sounds are heard on the normal side.[20] This could be produced by abnormal connections between the efferent and afferent parts of the cochlear nerve; and is seen in cases where hearing preservation is attempted but fails, using the middle fossa approach for a vestibular nerve section or an acoustic neuroma removal. If there is vascular damage within the internal auditory canal, the cochlear nerve, with or without cochlear damage, may be injured, allowing abnormal efferent and afferent regeneration. This can be thought of as the cochlear nerve corollary of synkinesis after a facial nerve regenerates. In this case, the cochlear nerve neuroma apparently also produced disabling tinnitus within the afferent cochlear nerve itself. Any treatment directed to the end-organ was useless. Translabyrinthine VIII nerve section is the most effective and thorough way of eliminating tinnitus caused by either an acoustic neuroma, a cochlear nerve or cochlear lesion.

TINNITUS MASKER

Patients with mild tinnitus who are troubled only when in a quiet environment are often satisfied by adding the background sounds of radio, television, a noisy clock, electric fan or special machines which will produce sounds such as waves breaking on the seashore. For patients with more severe tinnitus, three different types of instruments are available: 1) hearing aid, 2) tinnitus masker, 3) hearing aid and masker combination (Fig. 2). Saltzman and Ersner were the first to recommend the use of a hearing aid[24] in patients whose chief

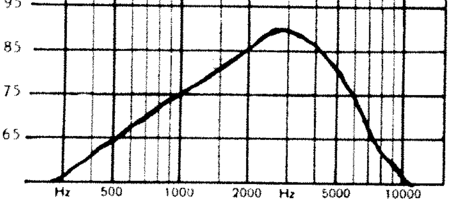

Fig. 4. High frequency tinnitus masker output. Coupler sound pressure level dB. RE: 20μ Pa.

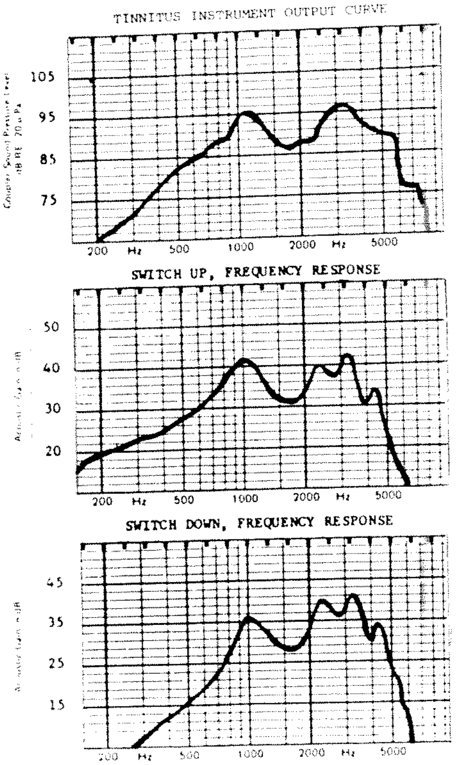

Fig. 5. Tinnitus intrument output curve.

complaint is tinnitus. The hearing aid selected is one which will give maximum relief of tinnitus; the improvement of hearing is secondary.

The tinnitus masker which is worn like a behind-the-ear hearing aid is available from the American Tinnitus Association. A wide band tinnitus masker (Fig. 3) and a high frequency tinnitus masker (Fig. 4) were used in this study. A masker alone is generally tried for patients with completely normal hearing or those who have useless hearing with poor discrimination. Patients with usable hearing who require amplification, as well as a masker, can benefit from a tinnitus instrument, which is a combination of a hearing aid and a tinnitus masker (Fig. 5).

Case 3. A 55-year-old, totally blind Caucasian male developed a head cold in July 1976, after which he had severely disturbing left tinnitus. He had tried many treatments, including biofeedback and a hearing aid, with no benefit. Hearing and tinnitus evaluations (Fig. 6) showed good hearing with a high

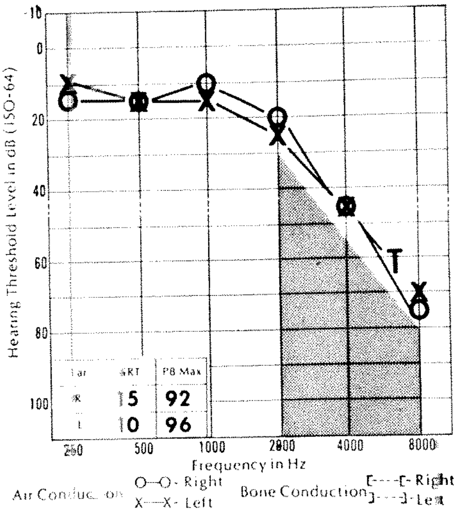

Fig. 6. (Case 3) A tinnitus evaluation with audiogram and area where tinnitus was matched (T). Shaded area represents masking used to relieve tinnitus.

frequency left tinnitus, which could be masked. A few seconds of residual inhibition was detected. A broad band masker with vented earmold was provided on July 7, 1977. The patient obtained complete relief of his tinnitus. He wears the unit all day and removes it at night. After using the masker for six or seven consecutive days, he will have one day of complete freedom from tinnitus without the masker. After wearing the masker successfully for almost one year, he finds his tinnitus much less disturbing and feels that the masker has helped him to cope with his tinnitus.

COMMENT: This patient represents one of our most dramatic successes with a masker. There is no evident explanation for the long period of residual inhibition which occurs periodically.

Case 4. A 60-year-old Caucasian male complained of severe fluctuating left high and low tone tinnitus for 16 years. He had worked in the shipyards in loud noise during World War II. Tinnitus evaluation (Fig. 7) revealed that the major low tone tinnitus could be relieved with a broad band masker; residual inhibition was from 20 minutes to one hour. He was fitted with a left broad band masker and has worn it since July 11, 1977.

COMMENT: This patient had two types of tinnitus. One was low pitched and very disturbing, the other was high pitched tinnitus, which was mild and of no concern. He was able to use his masker intermittently because of the significant residual inhibition.

Case 5. For three years, a 51-year-old Caucasian female had been complaining of a loud, disturbing noise in her head. The attacks were in cycles that lasted from five to eight days;

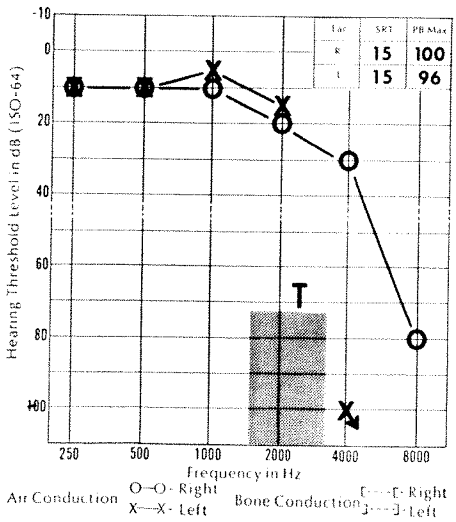

Fig. 7. (Case 4) Noise induced hearing loss. Left broad band masker effectively relieved tinnitus.

later the tinnitus became constant, with some fluctuation. She had previously had 12 sessions of biofeedback which, she felt, had made the tinnitus worse. Evaluation (Fig. 8) showed a high pitched tinnitus that could be masked by applying sound to either ear, but which was more effective when applied to the left ear. Brain stem audiometry revealed no abnormality on either side. A high tone masker was fitted for the left ear, and she has worn it since December 21, 1977, with excellent relief. She found that she could wear it one full day and remove it at night, following which she had only a very low nondisturbing tinnitus for two days without wearing the masker. On the third morning, she usually awakened with loud tinnitus which she controlled by wearing the masker.

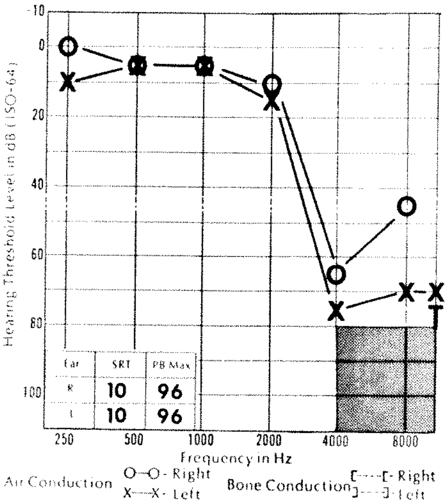

Fig. 8. (Case 5) Head noise. High tone masker used in either ear effectively relieved tinnitus.

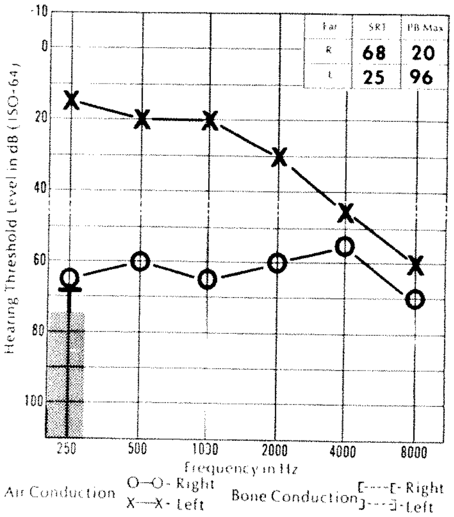

Fig. 9. (Case 6) Possible round window fistula. Right low tone masker effectively reduced tinnitus.

COMMENT: This may represent a central type of tinnitus, although it may have had its original origin in the left ear. Two full days of freedom from tinnitus represents the longest period of residual inhibition we have seen. This patient reported that she could hear a beeping noise from the masker when she wore it at home. The problem persisted, even with a replacement masker. After investigation, it was discovered that the maskers picked up the signal from radar equipment at the airport very near to her home.

Case 6. A 74-year-old Caucasian female complained of right tinnitus for five years. The onset of her symptoms occurred during a coughing episode; she felt her right ear pop with an associated sudden hearing loss, tinnitus onset, and vertigo. Her hearing remained poor and the tinnitus severe. Vertigo subsided in six weeks and positional and caloric tests were found to be normal. Békésy audiogram was type 2. A low tone tinnitus was found (Fig. 9), for which a broad band masker gave excellent relief. She has worn the masker since January 27, 1978.

COMMENT: The type of hearing loss, type 2 Békésy audiogram, and normal ENG suggest that the patient may have had a rupture of the round window and a perilymph fistula at the onset. The very poor speech discrimination made a combination of hearing aid and masker a poor choice.

Case 7. An 18-year-old Caucasian female

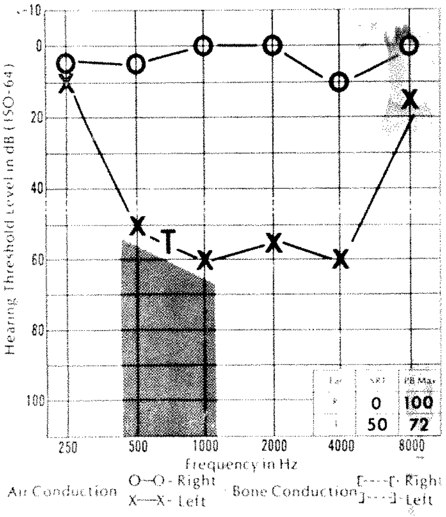

Fig. 10. (Case 7) Hearing loss and tinnitus from labyrinthine concussion. Tinnitus instrument gave best results.

was struck by a car on February 1, 1977. She sustained multiple injuries, and was unconscious for five hours. The patient was found to have a left hearing loss and a humming left tinnitus. Ten months after the accident, the tinnitus became much louder and very disturbing. It could be relieved by being in a shower or by the sound of a radio. Tinnitus evaluation (Fig. 10) revealed a low pitched tinnitus. An ENG demonstrated a right beating spontaneous nystagmus and normal caloric reactions. Petrous pyramid x-rays were normal. Both improved hearing and relief of the tinnitus were obtained by a tinnitus masker-hearing aid combination. The patient is pleased with the result, although she mildly objects to its appearance (Fig. 11).

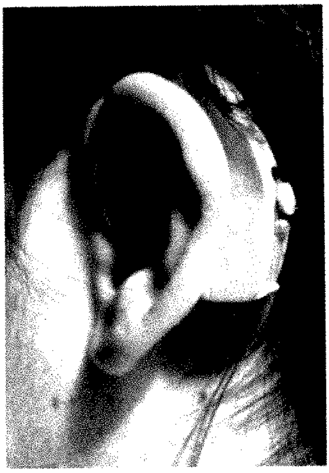

Fig. 11. (Case 7) Appearance of tinnitus instrument (masker and hearing aid combination).

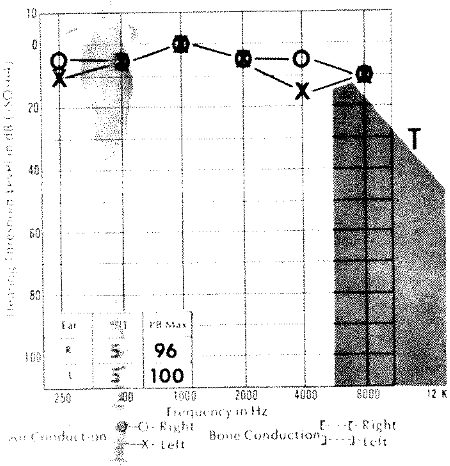

Fig. 12. (Case 8) Normal hearing with bilateral maskable tinnitus.

COMMENT: This patient most likely represents a labyrinthine concussion. The nature of her hearing loss made the combination masker and hearing aid the best choice. She had no residual inhibition or contralateral masking effect.[25] Although this patient had no difficulty adjusting the instrument, some elderly patients, or those with arthritis, have great difficulty manipulating the switches and volume control, because they are very close together. Redesign of this arrangement would be desirable. Development of all in-the-ear models should increase acceptability.

Case 8. A 28-year-old Caucasian male complained of bilateral high pitched tinnitus for eight months. He gave no history of other otologic diseases and was in good general health. Audiogram and ENG were normal. His problem could be relieved at night by running a small fan near his bedside. Tinnitus evaluation (Fig. 12) revealed that his tinnitus was at 12,000 Hz and could be masked when sounds were presented bilaterally. A tone 10 dB above threshold was effective. He had no contralateral masking effects. Although he could be masked very satisfactorily, he objected to the cosmetic appearance of the maskers and has elected to try biofeedback.

COMMENT: Tinnitus can occur in patients with normal hearing.[26] This patient could very well have the subaudible type of tinnitus, even though he complains that it is disturbing. The problem was not troublesome enough to warrant his wearing two maskers, even though they were effective.

BIOFEEDBACK

Although a form of biofeedback was developed by Hays[27] as a series of exer-

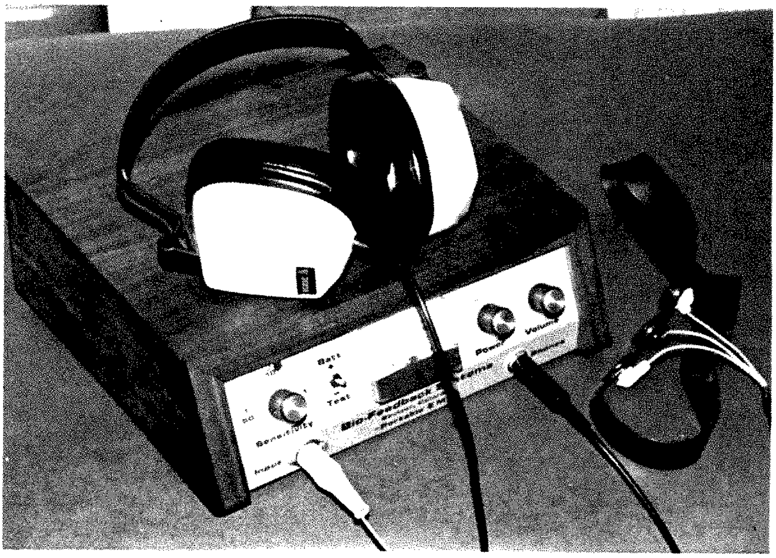

Fig. 13. Biofeedback treatment equipment.

cises in 1923, modern biofeedback has been used since 1972 to treat patients who fail to respond to standard medical management.[28-33] Biofeedback attempts to achieve muscle relaxation and increase circulation. An electromyographic device (Fig. 13)* allows the patient to experience the electrical output of the frontalis muscle by viewing the voltmeter, and by listening to clicks relayed to him through earphones. Most patients can learn muscle relaxation in six 20-minute visits. We have found this form of treatment to be most useful in patients who are very anxious about their symptoms and who seem to react far more than the tinnitus would warrant.

RESULTS

Of 950 new patients seen over a period of 18 months in an otologic practice, 64 had tinnitus as a major complaint. The diagnosis was undetermined in 30 patients: six had chronic otitis media, four acoustic trauma, three cervical vertigo, three Ménière's disease, and three labyrinthine concussion. Other problems were cochlear nerve neuroma, perilymph fistula, otosclerosis, labyrinthine ischemia, ear trauma, temporal bone fracture, facial palsy, otitis externa, cleft palate, metabolic disorder and sudden sensorineural hearing loss.

Tinnitus occurred in the right and left ears in equal numbers of patients (19 each). Tinnitus was present in both ears in 15 patients, and "in the head" in 11 patients. Fourteen patients had normal hearing, 18 had flat-hearing losses of varying severity, two had low-tone losses, 26 had high-tone losses, and four were profoundly deaf. Thirty-nine patients had sensorineural hearing losses, eight mixed hearing losses, and three had conductive hearing losses.

In 16 patients, the tinnitus produced insomnia; two patients were able to fall asleep, but were awakened by their tinnitus. Three patients were under psychiatric care.

Twenty-eight of the 64 patients underwent a thorough tinnitus evaluation. Twenty-three were maskable and five were not, an office success rate of 82%. The sensation level of the tinnitus, the level of loudness of the tinnitus above the patient's threshold of hearing, was less than 10 dB in 20, between 11 and 20 dB in 3, and between 21 and 30 dB in 4, and 30 dB in one patient.

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*Bio-Feedback Systems, Boulder, CO.

DISCUSSION

Introduction of tinnitus maskers has significantly increased our ability to relieve patients of disturbing, subjective tinnitus, it has sharpened our interest in the evaluation of tinnitus and research into the pathogenesis of subjective tinnitus. We have deduced that tinnitus can arise in the cochlea, the cochlear nerve, the brain stem, midbrain and cortex, since lesions confined to these areas can be associated with tinnitus. Moreover, the presence of tinnitus alone suggests that disease involving the auditory pathways can be present and a careful neurootologic examination should always be performed.

Characterization of the tinnitus is easier if the patient is asked to fill out a carefully designed questionnaire, and if equipment is available to match the patient's tinnitus, so that it can be more accurately described. A sweep frequency audiometer with one third octave narrow band masking is useful for this purpose. In addition, a tinnitus analyzer which can produce a variable width masking sound to determine the smallest band of sound which will mask the patient's tinnitus, is useful.

A multifaceted approach to the treatment of tinnitus, which can be tailored to the problem should be available. This includes the treatment of specific disease such as stapedectomy for tinnitus associated with otosclerosis, caused by a fixed stapes footplate, or an endolymphatic subarachnoid shunt for the endolymphatic hydrops of idiopathic Ménière's disease.[34] The identification and control of otologic allergy will sometimes solve the problem of tinnitus.[35,36] Foods are often the offending antigens and the cytotoxic food test is a valuable part of the examination. When hearing and vestibular function are not worth saving, translabyrinthine VIII nerve section offers a good chance for success.[20,34] Section of the cochlear nerve by the middle cranial fossa approach can be used in patients who have good vestibular function.

The fact that tinnitus can arise from any part of the auditory pathway means that each site will have a somewhat different pathogenesis. It is possible that several different mechanisms could occur within the cochlea. The mechanical cause is probably the most common. Although some controversy exists regarding the coupling between the stereocilia and the overlying gelatinous tectorial membrane, it seems likely that each stereocilia has a reasonably rigid connection to the tectorial membrane. Harris[illegible] calculated the effects of the Brownian motion of the air particles in front of the tympanic membrane upon the noise level at the hair cell input. He found that his calculations depended greatly on the degree of coupling between the hair cells and the tectorial membrane. For tight coupling, he obtained a noise level of minus 22 dB, in reference to the normal auditory threshold for 3,000 Hz, indicating that this threshold is given by the prevailing signal to noise ratio, as are most other such "thresholds." For loose coupling, Harris found the noise level at the hair cell input to increase to plus 33 dB in reference to the auditory threshold.

Using this information, Tonndorf[39] concluded that the increased noise level at the hair cell input, an increment of 55 dB, that is caused by the partial decoupling of the stereocilia from the tectorial membrane, ought to be perceived as tinnitus. In the case of acute episodes of endolymphatic hydrops, the static displacement of the basilar membrane produces a shearing displacement between the tectorial membrane and the organ of Corti. This static shear, he feels, should overextend the tenuous junctions between the stereocilia and the tectorial membrane. Tonndorf offers the explanation: "The Brownian motion in front of the tympanic membrane produces a broad-band noise. However, when the noise enters the cochlea its frequency components are distributed along the partition in accordance with the place principle. Decoupling is maximal in the region where the basilar membrane displacement is largest, i.e., the apical region. The noise must, therefore, be perceived as a band-limited, low frequency noise, i.e., as "roaring.""

Tinnitus might come about in exactly the same manner as just described in cases of noise trauma, labyrinthine concussion or from viral, vascular, metabolic or other injuries to the stereocilia. Bredberg et al,[40] with the aid of scanning electron microscopy, observed bleb-like lesions that formed on the apical ends of the cochlear stereocilia in cats after exposure to intense sound. Behavioral audiograms revealed a more profound hearing loss than seemed to be warranted by the sensory cell loss, demonstrated by light microscopy. He also showed other changes of the stereocilia of the hair cells, which consisted of fusion with reduction of size, or a complete disappearance of hairs. A fusion and growth of the stereocilia to "giant" hair cells was observed. Similar changes were observed in a sick cat, as well as in elderly human subjects. It is possible that the blebs when present on the stereocilia, partially decouple the connection between the tectorial membrane and the hair cells, and offers an explanation for tinnitus of mechanical cochlear origin.

A second mechanism which could produce tinnitus within the cochlea involves the injury, loss, or possibly even the injury and misdirected regrowth of the afferent and efferent nerve endings to the cochlear hair cells. Disruption of the complicated and multiple interconnections[41-43] between the nerves and the sensory cells could be expected to respond abnormally to any sound in a manner similar to the skin analogy studies of Békésy.[44]* An example of this type might be the patient who complains of recurring tinnitus during the time he hears the crackling of paper being crumpled, or the sound of a typewriter.

A third mechanism for the production of cochlear tinnitus involves the significant destruction of the cochlea and hair cells, usually as the result of a vascular injury that takes place spontaneously, or as the result of surgery to the vestibular nerve; not uncommonly in the few patients in whom the cochlear nerve and cochlea are left intact at middle fossa vestibular nerve section, or following middle fossa removal of an acoustic neuroma where the vascular supply to the inner ear is injured, an unusual type of tinnitus will develop.[20] Although these patients usually have total loss of hearing on the involved side, they will hear a loud tinnitus for a period of 15 to 30 seconds in that ear, which comes on a few seconds after the onset of hearing a moderately loud sound in the good ear. The tinnitus described by the patient has all of the characteristics of the cochlear efferent impulses analogous to the vestibular efferent discharges demonstrated by Goetmakers,[45] and the conduction velocity studies of Yagi et al.[46] It probably results in the pathologic synapse between the small cochlear efferent nerves and the large cochlear afferent nerves. Treatment for this type of tinnitus, when it is severe, is cochlear nerve section, medial to the spiral ganglia.

The cochlear nerve neuroma, or any other cerebellopontine angle lesion pressing upon the cochlear nerve, can discharge the nerve similar to other forms of compression. Another mechanism that has been proposed as the pathogenesis of idiopathic hemifacial spasm may be the erosion of myelin sheaths and a "cross-talk" between the cochlear efferent and afferent. Treatment is the removal of the tumor mass or excision of the cochlear nerve medial to the lesion.

The observation that exposure to loud noise will produce swelling within the ventral cochlear nucleus[47] could be used to support a theory that residual inhibition might be the result of changes in the cochlear nucleus. Some relation might be made with the idiophonic effect.[48]

Contralateral masking effect is only occasionally present. The significance of the crossed, inhibitory pathways between the ventral cochlear nuclei has been shown by Pfalz.[49] The reasons some patients can be masked contralaterally and others cannot, may be related to the site of the origin of the tinnitus and the integrity and effectiveness of the crossed inhibitory pathways.

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*Békésy, G. von: Personal communication to author.

Patients who have tinnitus associated with neurogenic cervical vertigo from a whiplash injury can obtain temporary relief by having their painful peripheral nerves anesthetized locally,[50,51] and can obtain permanent relief by a rhizotomy of the dorsal cervical rootlets of the involved nerves.[52] The excessive stimuli from the spinovestibular tract in cervical vertigo cases can produce tinnitus, as well as reduce cochlear function on the involved side by action directly to the cochlear nucleus. The VIII nerve or cochlea, need not be intact for tinnitus of this type to occur.

Tinnitus having its origin in the higher centers seems quite possible. A patient was observed by one of us (JLP), who had undergone singulectomy, a stereotactic neurosurgical procedure intended to improve a severe psychosis; she awoke from the anesthetic with a total, unilateral hearing loss and severe, persistent tinnitus. There were no vestibular symptoms and caloric reactions were completely normal. Subsequent translabyrinthine VIII nerve section had no effect upon the tinnitus.

Auditory hallucination seems to be caused by viral involvement or vascular lesions of the auditory cortex and is more common when there is an associated otologic lesion with one abnormal stimulus aggravating an area of injury.[53] Occasionally, a patient may continue to have disabling tinnitus on this basis following a cochlear nerve section, even though all the information clearly points to a solitary end-organ lesion. Myers[54] has suggested that tinnitus may become fixed centrally after it has persisted for a period of time. Our use of BERA and ECochG offers promise for our further understanding of the site of origin of tinnitus within the auditory pathways. We are currently studying the evoked brain stem response between stimulations in an attempt to measure tinnitus objectively and to study the characteristics of very short duration residual inhibition.

SUMMARY

The majority of patients with subjective tinnitus can now be successfully treated by the use of the hearing aid, tinnitus masker or combination hearing aid and masker. Tinnitus could be masked in 23 of 28 patients. All patients complaining of tinnitus should have a complete neurootologic examination to rule out serious disease and a tinnitus evaluation to establish the frequency, intensity and character of the sound, the site of origin and our ability to mask it. The pathogenesis and the medical and surgical treatment of tinnitus are discussed. Translabyrinthine VIII nerve section or labyrinthectomy is often effective for the relief of tinnitus associated with VIII nerve or cochlear lesions. A thoughtful and complete examination, using the new diagnostic tools, combined with the judicious selection of therapy, now makes it possible to give relief to the majority of patients with disturbing tinnitus.

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FROM THE EDITOR'S DESK

ANTIBIOTICS INDICATIONS DEVICE

Attention is called to AID$^{\text{TM}}$, a new Antibiotics Indications Device which was developed by Maxwell Finland, MD and an expert committee for Excerpta Medica Services. Every ear, nose and throat practitioner is confronted with the need for selecting proper antibiotics for the treatment of acute and chronic illnesses. He is confronted with the need to select the best antibiotic agent for that disease. AID provides a pocket-size, plastic device which indicates for each organism the antibiotic of choice, any supplementary drugs or alternate preparations in cases of bacterial resistance or patient hypersensitivity. Doses which are recommended in official compendia are listed.

AID should be in the top drawer of the desk of every physician who sees patients for primary medical care.

Ben H. Senturia, MD

Ann Otol 87:1978

SELECTED HEARING IMPAIRMENT ASSOCIATED WITH PINEALOMA

SCOTT N. REGER, PHD

IOWA CITY, IOWA

A 23-year-old Caucasian male entered the audiology clinic with a complaint of difficulty understanding speech, although speech sounds could be heard. Conventional clinical audiometry showed normal sensitivity bilaterally. The speech discrimination tests confirmed his inability to comprehend speech adequately. Békésy audiometer tests revealed dramatically rapid temporary threshold shifts bilaterally. Subsequent physical examinations revealed a massive pinealoma. Thirteen days after completion of Torkildsen's procedure, all the auditory tests indicated normal auditory function in each ear.

February 25, 1955 a junior year medical student entered my audiology testing laboratory and inquired if I could test his hearing for speech without the necessity of registering again in the Department of Otolaryngology. This student (RGH) was a Caucasian male 23 years of age at that time. The usual clinical pure tone audiometer test indicated essentially normal hearing in each ear. The conventional clinical pure tone audiometer test is equivalent to an interrupted type of test, but the speech discrimination score was 60% in the right ear and 56% in the left. Békésy audiometer tests with uninterrupted tones at discrete octave intervals showed the most rapid bilateral temporary threshold drift (TTD) up to that time.

A few questions revealed that he had appeared in the University of Iowa Student Health Services, from which he had been referred to Otolaryngology, Neurology, and Psychiatry. Since December 1954 he had been having occasional headaches, fluctuating hearing ability, occasional unsteadiness in walking and was having difficulties with his studies.

On January 3, 1955, he was examined by a resident in Otolaryngology who reported chronic faucial tonsillitis, headaches of unknown etiology, probably a tension type, and normal hearing as measured with the conventional clinical audiometer. The following day, January 4, the x-ray department reported an impression of bilateral maxillary sinusitis and questionable right ethmoid sinusitis, hyperplastic type. Two days later the Neurology Out-clinic reported normal vision, normal hearing with all other systems also normal.

As a result of these findings, Student Health Services referred RGH to Psychiatry, where he was undergoing treatment for an anxiety neurosis, agitated depression and typical medical student hypochondriasis.

As a result of the Békésy audiometer tests, I made a visit to the head of neurology and told him that RGH, as a result of Békésy audiometer and speech tests, had a significant hearing aberration, indicative of possible bilateral involvement of the acoustic nerves. He requested that the patient be sent to him as soon as possible and immediately changed his status to that of private patient so that he would be seen by heads of departments and senior staff members. For example, a radiology resident reported as late as March 18, 1955 that the films showed no localizing signs of tumor or disease; but, six days later, the head of the x-ray department reported that "ventriculograms demonstrated enlargement of the pineal, which indents the posterior margin of the third ventricle, and distorts

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From the Department of Otolaryngology and Maxillofacial Surgery, University of Iowa, Iowa City, Iowa.

Presented at the meeting of the American Otological Society, Inc., Palm Beach, Florida, April 23-24, 1978.

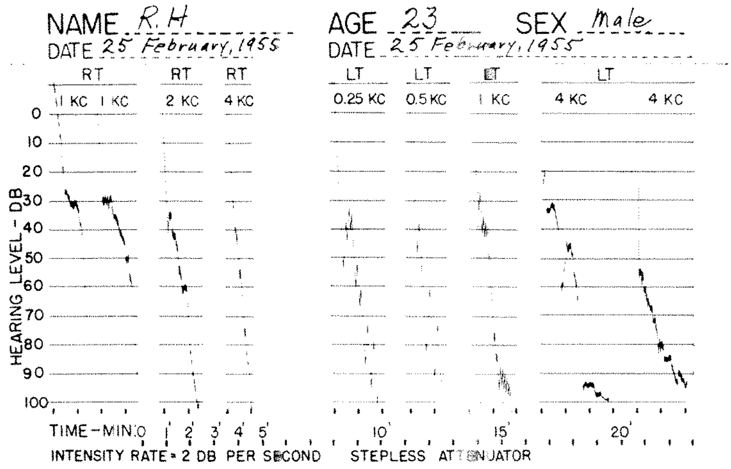

Fig. 1. Békésy audiometer test results before surgery.

the aqueduct, pushing it forward. There is symmetrical dilation of the lateral and third ventricles with nonvisualization of the fourth ventricle. Impression: Obstructive hydrocephalus due to a pinealoma."

After correlation of the several pertinent examinations and tests from various departments, also including Ophthalmology, the patient was referred to Neurosurgery. A suboccipital craniectomy with Torkildsen's procedure was performed March 24. The surgery was well-tolerated and the patient was awake and alert the following day. Radiation therapy was instituted two days after surgery using five fields — 2 lateral frontal and vertex and occipital — of 7 cm diameter, with the objective of a tumor dose of 5,400 rads.

X-ray therapy reported on May 14, 1955, that the "Patient completed treatment today having received 15 rounds of therapy for a tumor dose of approximately 5,400 rads. He has shown progressive improvement and tolerated therapy extremely well. He still has some trouble with his eyes which is due to unresolved hemorrhage. He has been able to return to school and carry a full work load." He completed an internship in a hospital in Milwaukee, married and is in general practice today — 24 years after surgery and x-ray treatment.

The early misadventures of this patient might be called a comedy of errors except for the fact it is not funny. It is of casual interest that the earliest indication of the seriousness of the case resulted from hearing tests with the Békésy and speech audiometers. Unfortunately, the hearing of the patient was not tested adequately when first seen in Otolaryngology, nor were vestibular tests administered on the initial examination.

Figure 1 shows the dramatic TTD

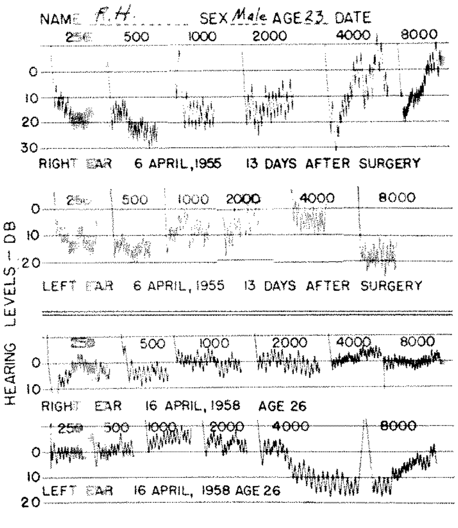

Fig. 2. Békésy audiometer test results 13 days after surgery (April 6, 1955), and comparable results three years later (April 16, 1958).

as revealed by the Békésy audiometer 27 days before surgery. Note the rapid slope at 250 Hz in the left ear. Figure 2 shows the postoperative measurements. The upper two sets of measurements show the results 13 days after surgery. The lower two sets of measurements show the responses a little over three years later.

The precise cause of the preoperative hearing aberrations remains conjectural but could have been due to stretching of the acoustic nerve, pressure against the nerve or partial interference with the blood supply to the nerve, or a combination of two or three of these conditions.

Hughes[1] lists 18 disease entities in which TTD may occur. Pineal gland tumors also belong in this group.

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THE CASSELBERRY AWARD of the AMERICAN LARYNGOLOGICAL ASSOCIATION

The American Laryngological Association announces that it will receive essays or theses relating to the art and science of laryngology and rhinology for consideration of the Casselberry Award for 1978-79. The award is open to scientists, physicians, interns, residents and graduate students in laryngology and rhinology in the Americas. *For information write*: William M. Trible, MD, Secretary, American Laryngological Association, 110 Irving Street, N.W., Washington, DC 20010.

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GUIDELINES OF GRANTS
TRUSTEES OF AMERICAN OTOLOGIC SOCIETY

A matter of continual concern to the members of the Board of Trustees of the American Otological Society is the determination of guidelines for the making of grants from its research fund. The following is our current formulation of policy.

Our objective is clearly before us as the problem of otosclerosis: its diagnosis and management, the possible causes and underlying conditions (such as the hereditary background), and an understanding of the disorder that may lead eventually to its prevention and cure.

Our present lack of understanding of the disorder and the absence, as far as known, of any similar condition in animals below man, make research in this field particularly difficult. A direct attack on the disease is hardly feasible; therefore it seems to be sound strategy to try circuitous approaches, such as the investigation of bone development, growth, and repair under various conditions, and the study of other diseases that show suggestive correspondence. It is possible that directions of investigation that may seem initially somewhat remote from otosclerosis itself may provide insights that will eventually lead to success in reaching our goal. The applicant should describe correlations between proposed research with the clinical pathological entity of otosclerosis.

Therefore, our policy is to aid and encourage research in the immediate field of otosclerosis and also in adjoining fields if in our considered opinion there is a substantial promise that the results obtained will be of assistance in the ways just indicated, and may lead to the attainment of our objective.

To stimulate the attainment of this objective, the Board of Trustees wishes to remind the general otolaryngologic community that funds are still available for suitable grants. Application forms may be obtained from the office of the secretary of the Research Fund Trustees of the American Otologic Society.

The grant request should be submitted by January 31, 1979, to David A. Hilding, MD, Secretary, 1300 Tower Road, Winnetka, IL 60093. Telephone (312) 441-5023.

Ann Otol 87:1978

CROSS-POWER SPECTRAL DENSITY ANALYSIS OF PURSUIT TRACKING

EVALUATION OF CENTRAL AND PERIPHERAL PATHOLOGY

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Twenty-one normal subjects were evaluated for pursuit tracking performance at frequencies of .2, .4, .8, 1.2 and 1.6 Hz. Measures of phase (lead or lag of target), gain (amplitude of response) and spectral purity (distortion of smooth tracking) were obtained by a cross-power spectrum analysis of the stimulus input and the eye movement output. It was determined that normal subjects could quite adequately track a target moving at .4 Hz. After establishing this parameter for normals, 43 patients with central and peripheral pathology related to the vestibulo-oculomotor system were tested at this frequency. Data revealed that not only central lesions but also peripheral labyrinthine impairment could cause a marked decrement in pursuit tracking ability. Also, marked changes in tracking were evident following both central and peripheral surgical procedures.

Although most clinical laboratories employ some type of pursuit tracking task in the overall evaluation of patients with vestibulo-oculomotor pathology[1,2] many of these tests involve only binocular tracking of a sinusoidal target or pendulum device. The data are then evaluated on a purely qualitative basis by looking for abnormalities (such as saccades) in the response. Although there have been quantitative studies of pursuit tracking, these have usually involved evaluation of only one parameter of the response (such as eye velocity[3] or latency of eye movement following target displacement[4]). The present test was developed to provide precise control over the input stimulus and to quantify the output in terms of phase, gain and frequency distortion.

METHODS AND MATERIALS

The stimulus was a small spot (15 minutes of arc) of red light from a helium-neon laser; this was reflected from a mirror galvanometer onto a rear projection screen. The galvanometer was driven sinusoidally in the horizontal plane at frequencies of 0.2, 0.4, 0.8, 1.2 and 1.6 Hz. The electronic drivers for the pen motors were developed in-house using solid-state amplifiers and equalization networks to provide a frequency response which was flat (±3 dB) from D.C. to 100 Hz.[5] This frequency response is far in excess of that required for this type of application. Departure from a flat response was not detectable over the narrow frequency range of 0.2 to 1.6 Hz which was used in this study.

The peak amplitude of the stimulus was 10° for all testing. The stimulus characteristics are given in Table 1. The subject's head was positioned both horizontally and vertically so that it was in the center of the screen. All recordings were conducted in the dark. A 15-minute waiting period to allow for changes in the corneal-retinal potential preceded each test. Eye movements were calibrated by driving the galvanometer system with a square wave input which produced a spot of light that moved a total of 10° in the horizontal and vertical planes. Eye movements were obtained under three conditions: both eyes tracking, left eye tracking and right eye tracking. Individual eye position and summated eye position were recorded by standard electro-oculograph (EOG) techniques on a Beckman Type RM Dynograph. The output of the dynograph was then fed to a digital computer for analysis. All EOG data were collected using a three-second time constant in the nystagmus couplers. This was done for two reasons. First, the drift produced by electrode polarization is minimized. This is important since the spectral

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The research reported in this paper was conducted by personnel of the Clinical Sciences and Biometrics Divisions, USAF School of Aerospace Medicine, Aerospace Medical Division, AFSC, Brooks AFB, Texas; the Otolaryngology and Neurosurgery Services, Wilford Hall USAF Medical Center, Aerospace Medical Division, AFSC, Lackland AFB, Texas; and the Department of Neurology, Audie Murphy V.A. Hospital, San Antonio, Texas. The voluntary informed consent of subjects used in this research was obtained in accordance with AFR 80-33.

Presented at the meeting of the American Otological Society, Inc., Palm Beach, Florida, April 23-24, 1978.

TABLE 1. VISUAL STIMULUS PARAMETERS

Stimulus Frequency (Hz)	*Peak Amplitude*	*Peak Velocity*	*Peak Acceleration*
0.2	10°	12.57°/sec	15.79°/sec^2
0.4	10°	25.13°/sec	63.17°/sec^2
0.8	10°	50.27°/sec	252.7 °/sec^2
1.2	10°	75.40°/sec	568.5 °/sec^2
1.6	10°	100.5 °/sec	1011 °/sec^2

Visual target is a spot of red light (632.8 nanometers) subtending an angle of 15′ at the observer. Target moves in the horizontal plane with a peak amplitude of 10° from center.

analysis program used does not remove trends (or drift) from the data prior to analysis and trends, if present, will cause aberrations in the calculated power spectra. Secondly, the need for the dynograph operator to constantly monitor and adjust the zero suppression controls during the test is eliminated. The effects of the three-second time constant and other filters in the system were corrected for by applying test sinusoids at each stimulus frequency to all three data channels simultaneously and analyzing the results with the computer. Phase and gain errors produced by the filters were then used to correct the data. These filter corrections were checked daily prior to data collection.

DATA ACQUISITION AND ANALYSIS

As mentioned, the EOG data were acquired using a Beckman Type RM Dynograph with Model 9859 nystagmus couplers. Four channels of analog data were simultaneously recorded using an Ampex FR-2000A FM magnetic tape system and digitized via the Nicolet MED-80 system. These data channels are: input stimulus (target position), summated eye position, left eye position and right eye position. The digitization rate of the MED-80 was adjusted according to the stimulus frequency so that data resulting from eight complete cycles of the stimulus presentation were digitized into 2048 samples. Thus, each of the four data channels occupies 512 memory locations in the MED-80. The system then computes the auto-power spectrum of each of the four data channels as well as the cross-power spectrum of the target position and each of the three eye position channels. The auto- and cross-power spectra allow for calculation of oculomotor system gain, phase and spectral purity (Fig. 1). Note that gain, phase and spectral purity are computed for each eye individually as well as the summated record for each of the three stimulus conditions. This results in a set of nine measurements of each parameter at each stimulus frequency. As shown in Figure 1, the system gain is determined by taking the ratio of the magnitude of the cross-power spectrum of the stimulus and eye movement out-

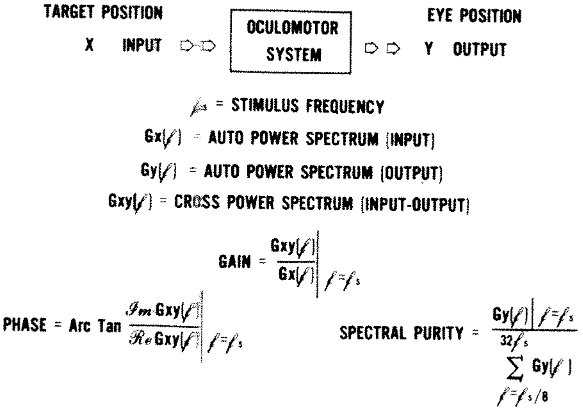
TARGET POSITION
X INPUT
OCULOMOTOR SYSTEM
EYE POSITION
Y OUTPUT
f_s = STIMULUS FREQUENCY
$Gx(f)$ = AUTO POWER SPECTRUM (INPUT)
$Gy(f)$ = AUTO POWER SPECTRUM (OUTPUT)
$Gxy(f)$ = CROSS POWER SPECTRUM (INPUT-OUTPUT)
GAIN = $\left.\frac{|Gxy(f)|}{Gx(f)}\right|_{f=f_s}$
PHASE = Arc Tan $\left.\frac{\mathscr{I}m\,Gxy(f)}{\mathscr{R}e\,Gxy(f)}\right|_{f=f_s}$
SPECTRAL PURITY = $\frac{Gy(f)|_{f=f_s}}{\sum_{f=f_s/8}^{32f_s} Gy(f)}$

Fig. 1. Flow chart indicating method of data analysis.

put (G_{xy}) to the auto-power spectrum of the stimulus input (G_x). This ratio is evaluated at the stimulus frequency (fs). Phase is calculated by taking the arc-tangent of the ratio of the imaginary part of G_{xy} to the real part, evaluated at fs. Spectral purity is defined as the ratio of the auto-power spectrum of the output (G_y) at fs to the sum of all the G_y values from 1/8 fs to 32 fs. Therefore, spectral purity is the ratio of the output power at fs to the total output power.

Normal Subjects. Twenty-one normal adult male and female subjects were evaluated to rule out any abnormality that might affect their pursuit tracking ability. These subjects had a mean age of 32 years with a standard deviation of 9.7 years and ranged in age from 18 to 57 years. Approximately one half of the subjects wore glasses but had normal visual acuity with correction.

Patients. The patients in this study were evaluated with both caloric and harmonic acceleration tests in a previous study.[6] All had received a complete neuro-otologic work-up prior to testing. Pursuit tracking tests were done prior to any vestibular testing.

Group 1 consisted of ten patients whose symptoms consisted mainly of dizziness. These patients had normal hearing. It was felt that these subjects would serve as a type of control group when compared to those with more definite pathology. They ranged in age from 16 to 67 years with a mean of 41 years and a standard deviation of 15 years.

Group 2 consisted of 18 patients with the clinical diagnosis of Ménière's disease. They ranged in age from 14 to 59 years with a mean age of 38 years and a standard deviation of 14 years.

Group 3 consisted of 11 patients with central deficits: 2 with brain stem infarction; 2 with multiple sclerosis; 2 with cerebellar degeneration; 4 with head trauma and 1 with basilar artery aneurysm. These patients ranged in age from 21 to 60 years with a mean of 41 years and a standard deviation of 14 years.

Group 4 was composed of four patients with acoustic neuromas. They ranged in age from 31 to 56 years with a mean of 42 years. These patients were tested before and after surgery.

RESULTS

If the oculomotor system tracks the stimulus in a linear manner, the spectral purity will equal 1.0. A spectral purity less than 1.0, for example 0.9, would mean that 90% of the output power of the system is described by the linear parameters of gain and phase; the remaining 10% is the result of nonlinear tracking behavior or noise. We found that in our 21 normal subjects the median spectral purity was greater than 0.95 for the summated record and greater than 0.85 for the individual eye recordings at the three lowest stimulus frequencies. At the highest stimulus frequency of 1.6 Hz, median spectral purity dropped to 0.75 due to increased saccadic activity. Saccadic eye movements and other eye motion that is inappropriate to linear system response will lower spectral purity. Since disconjugate eye movements and eye blink artifacts are rejected in the summated record, it will always show higher spectral purity than the individual eye recordings. In this study, the oculomotor system of normal subjects functioned in a linear fashion in the performance of this particular tracking task. Data from the normal subjects indicated that the gain and phase measures described oculomotor system performance quite well at the three lowest stimulus frequencies and accounted for >95% of the power in the summated record and >85% of the power in the individual eye recording for each stimulus. One would therefore assume that decrements in oculomotor performance should be reflected as changes in gain and phase that would deviate from the normal values. Also, if the performance decrement manifests itself as a departure from linear system operation, then the spectral purity should show a decrement.

An analysis of variance indicated that the spectral purity, gain and phase did not differ among the three tracking

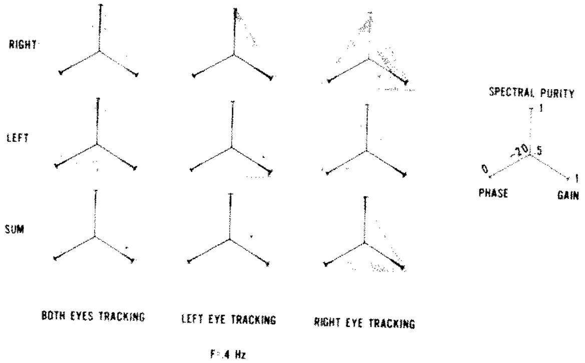

Fig. 2. Data from 21 normal subjects. Shaded area indicates the 10th and 90th percentiles.

conditions in our normal data; i.e., the same results were obtained for both eyes tracking, left eye tracking, or right eye tracking. Spectral purity showed a significant difference ($P<.001$) between the summated record and the left and right eye recordings at all frequencies. This was to be expected, since the summated record contained less noise and eye blink artifact than the individual eye recordings. The phase measures showed no significant differences among the three records (within 2° except at 1.6 Hz which was 5°). Spectral purity did not show a significant difference between the left and right eye recordings. There were no interactions between tracking conditions (both eyes, left eye or right eye) and the eye movement data (summated, left or right eye position).

The gain data showed the greater variability since it was subject to calibration errors, whereas the phase and spectral purity were, by definition, independent of scale factor or calibration errors. Calibration errors in our system were estimated to be on the order of 10% (2° of eye movement). Thus, statistical variability in the gain data of 10% or less can be attributed to calibration error. In addition, vertical eye movements or disconjugate horizontal eye movements will affect the gain in the individual eye recordings but will be rejected by the differential recording of the summated technique.

Our normal data showed gains close to 1.0 and phase shifts around 0° at stimulus frequencies of 0.2 and 0.4 Hz. Considering the fact that a sinusoidal stimulus is a deterministic function (i. e., its future course can be predicted), our results are not surprising. Unity gain and zero phase lag results from anticipatory tracking behavior. The use of a pseudorandom or random-appearing stimulus would certainly lead to an entirely different set of gain and phase data. Normal everyday visual tracking requirements typically involve a target whose trajectory is predictable to a significant degree. Therefore, we have concluded that an assessment of pursuit tracking should be performed using a deterministic stimulus.

We found the pictorial analysis as shown in Figure 2 to be most useful. This type of presentation permits rapid comparison of gain, phase and spectral purity of each eye and the summated recording under each of the three tracking conditions. To permit comparison of each subject to our normal data the 10th and 90th percentile of each parameter were superimposed on each axis as indicated in Figure 2. Perfect tracking (a gain of 1.0, phase of zero, spectral purity of 1.0) would result in a set of nine equilateral triangles. The actual performance of normal subjects results in a slight skewness of the triangles.

Pursuit tracking appears to be a very sensitive test of unilateral impairment; as a result, patients with the same clinical diagnosis may produce completely

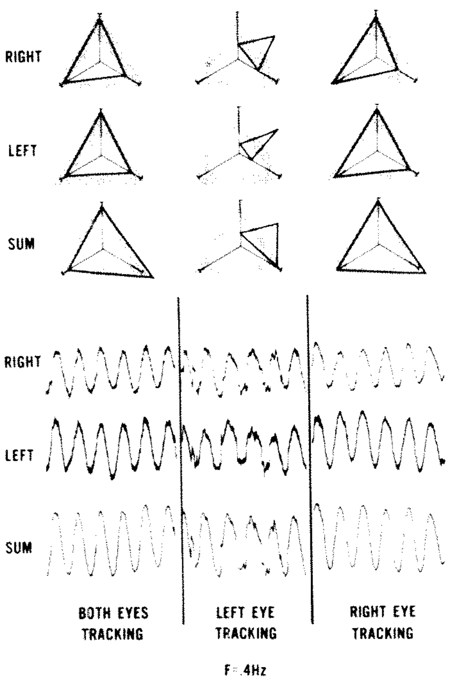

Fig. 3. Raw data and computer analysis from a patient with a pontine infarction.

different patterns of response. Therefore, it does not appear meaningful to collapse data across subjects.

CASE REPORTS

Case 1. A 53-year-old male was evaluated two months after suffering an infarction clinically diagnosed as being in the pontine reticular formation. As shown in Figure 3, the raw EOG tracings indicated essentially no difference between the left and right eye when tracking with both eyes open. However, when the right eye was occluded (left eye tracking), there was an obvious decrement in the quality of the tracking which showed saccadic movements and a departure from a sinusoidal waveform. Tracking with the right eye appeared to be slightly better than when tracking binocularly. Computer analysis of these responses (Fig. 3) revealed a marked decrement in all three measures when the left eye was tracking. The decrement in spectral purity can be ascribed to the increased saccadic eye movements. But, more importantly, the underlying sinusoidal component, as described by gain and phase, shows significant decrements with phase showing a 20° lag. This marked change in gain and phase is not readily apparent in the raw record as the saccadic activity tends to mask the sinusoidal component. At best, phase shifts of 15 to 20° are difficult to see in an ideal raw record.

Case 2. A 56-year-old male had the acute onset of a horizontal diplopia on right gaze. He was referred to an ophthalmologist to determine if he had a "tight rectus muscle" or possibly an internuclear lesion. It was apparent on gross examination that his left eye had restricted movement when looking between two objects. When evaluated on the pursuit tracking test he revealed a much more complex interaction in his oculomotor response. As shown in Figure 4, binocular tracking confirmed a decrement in the gain of his left eye. However, when his right eye was occluded (left-eye-tracking), the left eye showed an increase in gain (slightly greater than one) and the quality of the left eye tracking improved (higher spectral purity) although it did show an increase in lag in reference to the target. Under this same condition, the right eye reflected twice the gain of the left even though it was moving at the proper frequency and was in-phase with the stimulus. When tracking with the right eye only, there was a complete absence of the previous asymmetries with only a slight decrement in the spectral purity of the left eye.

Case 3. A 44-year-old male had a 2½ cm tumor removed from the right side. The tumor was firmly attached to the brain stem just below the V cranial nerve; it indented the pons

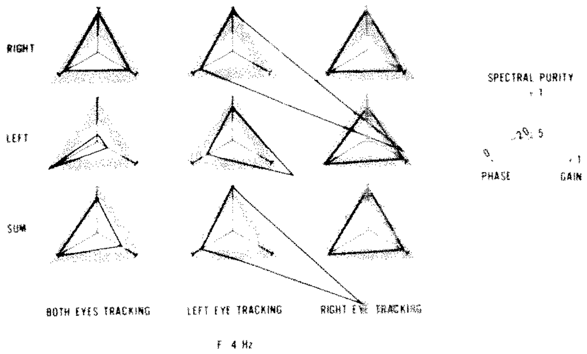

Fig. 4. (Case 2) Data from patient with a sensorimotor lesion.

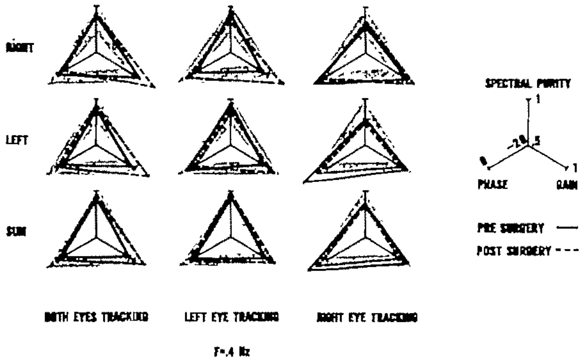

Fig. 5. (Case 3) Data from patient with a right 2½ cm acoustic neuroma; solid line indicates presurgery test.

but did not appear to be compressing the cerebellum. Figure 5 shows pre- and postsurgical tracking data from this patient. His greatest decrement prior to surgery was evident when he was tracking with his right eye; both eyes showed a decrement in the spectral purity and a phase lead in reference to the target. The fact that the summated record is very similar to the independent eye recordings indicates that the eyes were moving conjugately, but inappropriately in response to the input. This patient was again tested seven days following surgery. The only evident changes in his tracking at that time were an increase in the gain of the right eye under all conditions and an improvement of the phase relationships when tracking with the right eye. When re-evaluated five months postsurgery he had almost perfect tracking under all conditions.

Case 4. A 49-year-old male had a five-year history of typical symptoms of Ménière's disease in the left ear. This patient was evaluated before and after a left endolymphatic shunt procedure. Figure 6 shows pre- and postsurgical data. With binocular tracking, he showed a lead in both eyes and a decrement in spectral purity and gain in the left eye. Tracking with the left eye showed a marked impairment in the gain and spectral purity of the left eye (compared to the normal range); the right eye reflected only a slight decrement in gain and spectral purity. Tracking with the right eye also led to a greater decrement of the left eye. This patient was retested seven days following the shunt procedure, and his binocular tracking was within normal limits. Although he showed a slight decrement when tracking with his left eye, there was still a rather dramatic improvement in his performance. Tracking with the right eye showed only minimal improvement over his preoperative test results.

DISCUSSION

Most clinical research efforts have evaluated sinusoidal pursuit tracking by qualitative analysis of the raw records of pendular tracking. We have attempted to provide an analysis of pursuit tracking using power spectral techniques to "read" the records and provide numbers for evaluation. Our data, and data from other studies,[2,3] indicate that

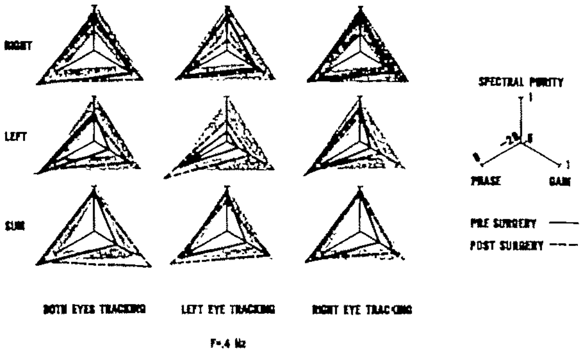

Fig. 6. (Case 4) Data from patient with Ménière's disease before and after an endolymphatic shunt; solid line indicates presurgery test.

normal individuals track smoothly with stimulus frequencies up to 0.4 Hz. Beyond 0.8 Hz increasing saccadic activity begins to degrade smooth tracking performance. Since the main object is to evaluate patients who are suspected of having oculomotor pathology, the test should be one that can easily be accomplished by normals.

There are a number of problems that exist with independent recordings of each eye: the electrodes must be carefully placed in line with the dipole of the eye; eye movements in any direction will be recorded; disconjugate movements and eye blinks will appear in the records. However, the summated record serves as an overall standard for comparison; i.e., if one sees an abnormality in the summated response that is closely correlated with one eye, it is highly probable that the independent recording is a fairly accurate representation of the eye movement response.

The fact that peripheral vestibular impairments can affect pursuit tracking is not a new discovery[1] and is not surprising since it is obvious that changes in input to the vestibular nuclei are going to influence the neural patterns in the oculomotor nuclei and eventually the lateral and medial rectus muscles. We found that 90% of our patients who had a nonspecific diagnosis of vertigo had perfectly normal pursuit tracking, while patients with typical symptoms of Ménière's disease had tracking impairments that were usually related to the involved side. All of the patients with central pathology showed severe impairments when tracking monocularly.

It is obvious from our data that the use of only binocular recordings or tracking with both eyes open will not give an adequate evaluation of oculomotor impairments. The visual system appears to compensate for central and peripheral deficits by suppressing the affected side and allowing the "best" neurological pathways available to control the eye movements. This assumption is clearly supported by cases 1 and 2; the binocular recording alone does not reveal the complete situation. Unfortunately, we are trained to believe that the eyes move conjugately and continue to apply this interpretation to patients with obvious unilateral pathology. The simple addition of monocular tracking trials to any pursuit test will greatly enhance the clinician's ability to diagnose oculomotor pathology. This is true even if only summated horizontal eye movements are being recorded.

We have been impressed with the complex changes in innervation that can occur in response to monocular stimulation. In this regard, perhaps monocular optokinetic stimulation would reveal some of these deficits. Only one of our patients (case 2) had grossly asymmetrical optokinetic responses with binocular vision. Since these patients were also given complete caloric and harmonic acceleration evaluations, time did not permit monocular optokinetic evaluation. However, our data suggest that this would be a meaningful clinical evaluation.

SUMMARY

Cross-power spectrum analysis of simple pursuit tracking provides an intricate analysis of the oculomotor reflex which can aid the otologist and neurologist in the evaluation of patients with oculomotor abnormalities. Our method of data presentation should be useful in evaluating these responses since numbers are reduced to meaningful patterns. Hopefully, this method will contribute to a better understanding of the neural pathways which subserve vestibulo-oculomotor function.

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CLINCAL USE OF PSEUDORANDOM BINARY SEQUENCE WHITE NOISE IN ASSESSMENT OF THE HUMAN VESTIBULO-OCULAR SYSTEM

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White noise rotational stimulation has been used to evaluate the human vestibulo-ocular response for 30 normal subjects over the frequency range from 0.02 to 1.6 Hz and is being extended to characterize response of patients having documented abnormalities. For clinical use, the white noise stimulus has the advantages of shortening the test time by presenting all stimulus frequencies simultaneously, and being well-tolerated by both normal subjects and patients alike. Cross spectral calculations which compare the computer reconstructed slow phase eye velocity response to the pseudorandom acceleration stimulus yield a set of linear and nonlinear estimates of the vestibulo-ocular response. Pilot data indicate that a classification of the disease state can be made using this set of estimates. This classification will be presented and discussed.

A century of clinical and investigative effort has returned parsimonious practical benefits for testing the vestibulo-ocular system. There are no universally accepted, much less standardized, clinical methods for evaluation of the human vestibulo-ocular system. In contrast, clinical methods for assessment of auditory function have developed at a far greater pace. Auditory function tests developed with the aid of interested psychologists and psychophysicists; until recently, most of the clinical audiologic examinations were basically applied psychophysical methods. Vestibular system researchers on the other hand, dealt primarily with muscle reflexes elicited by vestibular stimuli. Vestibular responses, governed by numerous converging inputs many of which are difficult to control, provided additional challenges to both basic and clinical investigators when extraterrestrial exploration began.

A quantitative, efficient approach to testing and analyzing the human vestibulo-ocular reflex (VOR), based upon fundamental and recent advances in biophysics, bioengineering and otology, has proven successful in pilot studies.[1] This paper outlines initial experience with the clinical application of a novel and highly successful research method of vestibular system evaluation.[2-7]

Although of great historical interest and conceptual importance to this study, a detailed review of research on the VOR prior to employment of systems and control theory approaches would be redundant. There are many excellent reviews which are obligatory reading for those interested in vestibular system physiology and especially the VOR.[8-18] A brief review of conceptual models and the technical developments which have enabled assessment of those models will provide a background for the rationale of the present VOR test approach.

Late in the 19th century Ewald,[19] Crum-Brown,[20] and early in this century, Bárány[21] demonstrated that unidirectional angular acceleration of the head caused a contralateral rotation of the eyes followed by an ipsilateral saccadic "correction" (nystagmus). These and many subsequent investigators established the fact that vestibular input was required for initiation of this reflex. The

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descriptive name for this physiological action, the vestibulo-ocular reflex, has survived extensive neuroanatomical, neurophysiological and psychophysiological studies.[8,9,11,13,15,17,18,22-28]

For almost 75 years following the work of Crum-Brown, Mach,[29] and Ewald on the VOR, deterministically modulated rotation stimuli (e.g., sinusoidal angular accelerations) were employed to study the VOR system. Descriptions of VOR system characteristics in the frequency or time domains required laborious, meticulous, time-consuming, experimental protocols and analysis methods which often yielded conflicting results.[30-34]

Quantitative methods for systems identification of vestibular responses developed rapidly when mini- and microcomputers became commercially available. This key development in computer technology combined with advances in motion control hardware enabled the following important advances in vestibular physiological techniques:

Stimulus Control. The study of peripheral vestibular function is basically a study of motion signal detection and transduction. Consequently, design of instrumentation capable of simultaneously presenting accurately controlled position, velocity and acceleration stimuli through sufficiently wide frequency ranges to human subjects in years past, was either technically impractical or prohibitively expensive. Development of the required peripheral hardware by individual laboratories was time-consuming, expensive, and once completed often became quickly obsolete. An important technical development occurred when high torque servo controlled rate-of-turn tables were successfully interfaced with programmable minicomputers for precise motion control.

Response Signal Analysis. Sensory system physiologists studying human vestibular responses relied heavily upon traditional psychophysical methods for quantitation of sensory input-output relationships. Predictably, attempts to employ basic techniques developed for other sensory systems (e.g., the auditory system which projects extensively to the cerebral cortex) for the study of the vestibular system (which has a comparatively limited cortical projection) responses met with limited success. The cupulogram[35] is an example of a vestibular test that never became a widely acceptable clinical test of vestibular function.

Early vestibular physiologists soon realized that the vestibular system, in contrast to the auditory and visual systems, projected primarily to muscle control systems with comparatively sparse connections to the cerebral cortex.[36] Upon discovery of the corneoretinal potential as a convenient method for objectively recording a vestibular reflex, a lagging interest in the vestibular system revived because a relatively simple recording technique permitted quantitation of input-output relationships with reasonably good resolution in comparison with psychophysical methods. This important advance permitted more thorough studies of the torsion pendulum VOR model.[37] These models worked moderately well for sinusoidal inputs, but output analysis problems developed because of inherent nonlinearities in nystagmus waveforms.[38] Difficult to control variables such as fluctuating nystagmus parameters due to reverie, and response habituation with repeated deterministic stimuli also created analysis problems and complicated development of both conceptual and mathematical models of the VOR.[39-42] (Parenthetically, it should be mentioned here that nystagmus elicited by vestibular stimulation does not necessarily imply that the VOR system is behaving nonlinearly.)

The development of computerized signal analysis removed some of these problems.[43-45] A computerized nystagmus analysis technique has been developed and successfully employed in both animals and humans in our laboratories.[1] The interactive computer programs developed in our laboratories also may be used in a batch process mode which frees laboratory personnel for other duties.

Input-Output Determinations. Accurate VOR transfer functions were difficult, laborious, and time-consuming to obtain even with the aid of computers until the development of on-line and interactive off-line analysis techniques in our laboratories.[5,6] Simultaneous control of input with on-line or immediate off-line statistical analysis of response performed by computer algorithms allowed the development of an efficient, information-rich method of vestibular system evaluation.[1,3] These programs provide both time domain ("impulse" responses) and frequency domain (gain and phase) response parameters from which a mathematical input-output summary (transfer function) can be obtained. These data can be treated statistically for quantitative comparison of normal versus abnormal populations or, as suggested in the following section, pathological versus adaptive behavior.

The remarkable VOR plasticity described by Melville Jones and colleagues has directed the thoughts of many researchers and clinicians toward new ideas in modeling.[46,47] This redirection in turn has resulted in a new burst of activity and research into the vestibulo-ocular reflex control systems, especially hierarchical control systems. The use of computers for applications of systems and control theory techniques are thus required for the development of adequate conceptual and mathematical VOR models and for the accumulation of data sufficiently resolute for the study of complex vestibulo-ocular responses. This paper describes our preliminary experience with VOR responses to pseudorandom binary sequence (PRBS) rotational stimuli as a clinical method.

The use of white noise acceleration stimulus and linear systems analysis as an effective method of clinically evaluating human vestibulo-ocular reflex (VOR) for normal subjects has recently been demonstrated.[1] The present report examines a clinical effectiveness of the linear system approach in pilot studies of humans having pathological VOR responses. The linear system predictions of gain and phase, when used in conjunction with measures of system asymmetry allows the differentiation of three classes: normal, reduced unilateral responses with indication of weaker side, and reduced bilateral response.

METHODS AND MATERIALS

Human rotational tests were performed using a steel chair mounted on a computer-controlled torque motor. The computer delivered stimulus consisted of an eight-stage PRBS,[48] using a state duration, $\triangle t$, of 200 msec and a $40^\circ/\text{sec}^2$ acceleration which provides a stimulus bandwidth of 0.02 to 1.67 Hz. Outer canthal surface electrodes were used in conjunction with suitable amplifiers and filters (0-30 Hz) to record the VOR nystagmus response to acceleration stimuli. Data were digitized and subsequently off-line analyzed using an interactive computer program. The methods have been described in more detail elsewhere.[1,3]

The eye movement response (nystagmus) to a rotational stimulus is a sawtooth-like waveform. One half of each sawtooth is a compensatory eye movement having a slope which relates to the rotational stimulus (the slow phase of nystagmus). The second half or fast phase is a quick reset motion to reposition the eye. Although the fast phase is related to stimulus amplitude and frequency,[38] the information in the slow phase is given primary priority in the present analysis technique. The first task of a computer program is to interpret this nonlinear process by determining the eye velocity during the compensatory slow phase movement while estimating this velocity by extrapolation during a reset phase of the response.

The resulting waveform is referred to as reconstructed slow phase velocity (SPV) and is the input to the algorithm which determines the linear systems parameters of gain and phase by cross spectral calculations.

It is important to distinguish between this inherent nonlinearity that is essentially eliminated by the SPV reconstruction algorithm and other nonlinearities which can be caused by such factors as asymmetrical vestibular response. Information derived from the reconstructed SPV can be used as a measure of asymmetrical vestibular performance.

Transfer function and coherence were computed by the following method. Let $S_x(f)$ and $S_y(f)$ be the Fourier transforms of the PRBS input and the reconstructed eye velocity output respectively. The auto- and cross-power spectra are given by

$$G_{xx}(f) = S_x(f)\ S_x^*(f)$$
$$G_{yy}(f) = S_y(f)\ S_y^*(f)$$
$$G_{yx}(f) = S_y(f)\ S_x^*(f)$$

where * denotes the complex conjugate.

The transfer function of slow phase eye velocity to white noise acceleration is given as

$$H(f) = \frac{G_{yx}(f)}{G_{xx}(f)}$$

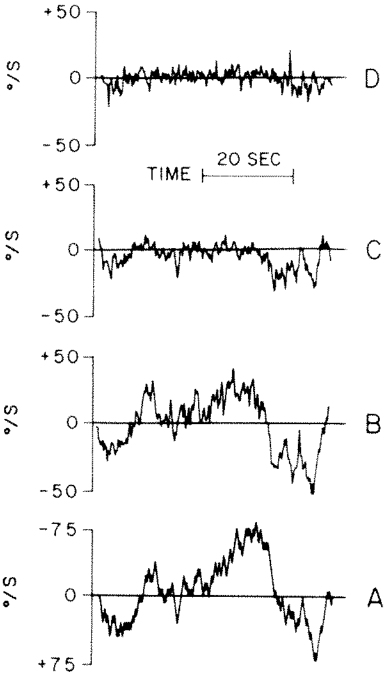

Fig. 1. A) Single 51.0 period rotational chair angular velocity response to a PRBS white noise acceleration stimulus. Stimulus switches between +40 and −40°/sec^2. Velocity profile has mean value of 0.0 and peaks of +80 and −80°/sec. B) The reconstructed SPV taken from the vestibular ocular reflex response of a normal subject performing mental arithmetic recorded using bitemporal electro-ocular electrodes. Response averaged over five periods of white noise stimulus. Response is compensatory in direction and mimics the overall shape of the velocity profile, A. Mean value of the response is 0°/sec. C) The response similar to that in B but taken from a patient having only one vestibular labyrinth intact. Response still has some of the overall shape characteristics of A, but is smaller in magnitude and has a mean velocity value of −7°/sec. D) Response from patient with a large acoustic neuroma and who displayed no response from caloric stimulation of either labyrinth. The response is markedly smaller than normal and has no features which are easily correlated with the velocity profile, A.

which can be separated into magnitude and phase components. The coherence function used test system causality is defined as

$$\gamma = \frac{G_{yx}(f)^2}{G_{xx}(f)\ G_{yy}(f)}$$

The range of the function is zero to one where the value of one implies perfect causality, i.e., that the output is linearly related to the signal input having no noise contamination or nonlinearity. Confidence intervals may be derived from the coherence function and the input and output power spectra as described by Bendat and Piersol.[49]

RESULTS

Slow Phase Velocity Response To White Noise Input. The typical normal slow phase reconstruction shown in Figure 1B is compensatory in direction, has a zero mean value, and has the shape of the stimulus velocity profile (Fig. 1A). For 30 normals, the mean slow phase velocity was −0.10°/sec. The standard deviation of ±1.19°/sec and a maximum deviation of 3°/sec. The one-sided response (Fig. 1C) (left labyrinthectomy in a 60-year-old male after approximately one year) is somewhat smaller in magnitude than the normal response and has a −7°/sec. mean value.

This deviation is more than twice the largest normal deviation and implies a vestibular system bias to the right due to removal of the left labyrinth. This is in agreement with the vestibulo-ocular response in labyrinthectomized monkeys[31] which shows a marked one-sided bias that eventually diminishes[50] as the vestibular system adapts to a one-sided input. This bias is an indication of a nonlinear output due to the asymmetrical vestibular input to the VOR. Our preliminary data from patients having right labyrinthectomies display a bias in the opposite direction. The patient having reduced bilateral response to caloric stimulus due to severe brain stem compression by an acoustic neuroma has a small, noisy, reconstructed SPV with zero mean and very little signal content that visually correlates to the stimulus velocity.

Linear Systems Estimates. The relatively high values of the first four coherence measures from 0.02 to .23 Hz for typical normal VOR response, indicates that the linear system frequency domain gain and phase parameters characterize the response over that bandwidth fairly well. This is further confirmed by noting that changes in the stimulus strength by a factor of two

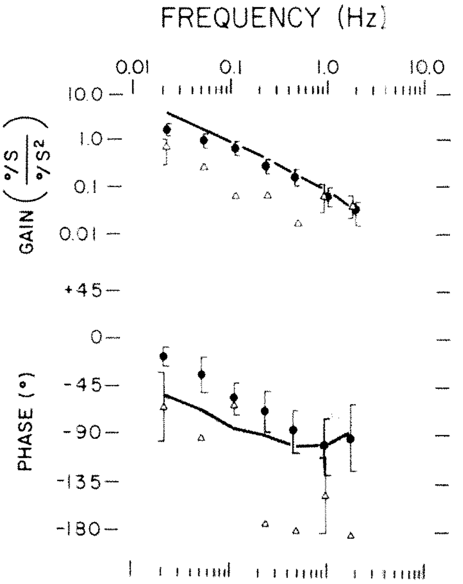

Fig. 2. Gain and phase responses of the SPV component of the vestibulo-ocular reflex to white noise acceleration using cross spectral calculations. Thick solid lines surrounded by shaded area represent mean value ± one standard deviation for 30 normal subjects. Circles with left facing brackets show mean estimates with 95% confidence intervals for a patient having a unilateral labyrinthine response (Fig. 1C). A first gain point is lower than normal and the first three phase estimates are all higher than normal; relatively small confidence intervals due to coherence values greater than or equal to 0.5. Triangles with right facing brackets show mean estimates with 95% confidence intervals for a patient having no response to caloric stimulation of both labyrinths (Fig. 1D); confidence interval not plotted when the limits exceed the gain estimate itself. First gain point is approximately one tenth that of normal value and all gain points fall below normal value.

affected the transfer function by less than 10%. An increase in stimulus strength resulted in a slight increase in transfer function gain values and a slight coherence increase. The opposite effect was observed when the stimulus strength was reduced by a factor of two.

Figure 2 contrasts the gain and phase of normal subjects with the abnormal pilot data. The patient having a one-sided vestibular response shows gain slightly less than normal at the first frequency point which is shown as a dark circle with 95% confidence limits at 0.02 Hz. The coherence value for this response is slightly lower than those of a normal. The remaining gain points are not significantly below the normal values, however the corresponding phase points show significantly less lag than the normal data in the region from 0.02 to 0.1 Hz. For the patient having reduced bilateral response (open triangles) the first gain point at 0.02 Hz is significantly below that of normal. Although the 95% confidence intervals for the rest of the points exceed the gain estimate, the next five gain estimates all fall below normal limits. Due to the large noise value nothing significant using 95% confidence intervals can be stated about the phase response from this patient.

Thus the two classes of abnormal response can easily be distinguished from normal by using a combination of linear and nonlinear estimates as shown in Table 1.

DISCUSSION

The PRBS stimulation technique combined with linear system analysis has many advantages as a clinical test of the human VOR. These include:

1. Marked reduction in test time with much greater information yield. The entire PRBS protocol can be run in seven minutes. There is a time savings of at least 20 minutes over the sinusoid protocol reported by Wolfe et al.[51] Instead of a single frequency point, many frequency points along with a statistical estimate of their reliability can be computed. Moreover, all frequency points are obtained under similar conditions of alertness and corneoretinal potential amplitude thereby minimizing procedural artifacts.

2. Low amplitude acceleration inputs can be used thereby reducing motion sickness. None of the normal or abnormal subjects tested to date have experienced discomfort of any sort during PRBS stimuli. An acceleration ramp of 5°/sec² x 10 sec delivered as a pretest familiarization stimulus produced dis-

TABLE 1. TEST PARAMETERS

Class of Abnormality	*Gain*	*Phase*	*Coherence*	*Mean SPV*
Asymmetric				
Weak right	Normal or slightly below normal	Significantly above normal	Slightly lower than normal	>3°/sec
Weak left	Normal or slightly below normal	Significantly above normal	Slightly lower than normal	<−3°/sec
Reduced bilateral	Well below normal	Not systematically distributed	Much lower than normal	

comfort (diaphoresis, slight nausea) in some subjects, both normal and abnormal and was therefore discontinued.

3. Subjects can neither anticipate nor predict PRBS stimulus direction. This characteristic of the technique appears to reduce adaptation and response decline significantly.

The detection of VOR asymmetry in the reconstructed slow phase velocity response to PRBS acceleration offers many advantages. But there is an additional advantage over the caloric method of detecting a one-sided weak vestibular response: An equal stimulus is delivered to each labyrinth. In caloric stimulation, response differences between sides of up to 30% are considered to be within normal limits due primarily to variations in stimulus application technique and differences in thermal conduction paths from the two external ear canals to the labyrinth. The present white noise measure of asymmetry is an estimate averaged over the test bandwidth of 0.02 to 1.67 Hz. The harmonic (sinusoidal) technique estimates the asymmetry as a function of frequency. There are potential advantages to each approach and one estimate may be more sensitive to asymmetry than the other. These possibilities are presently under investigation in our laboratory.

For the categories which we have chosen, a linear system analysis plus a simple measure of asymmetry using the PRBS technique appears to provide an efficient, objective method of identifying VOR status in patients with unilateral and bilateral labyrinthine defects.

We presently do not have enough experience to determine or identify responses that are both asymmetrical and bilateral or to determine the degree of asymmetry in a person having bilaterally reduced responses. We are unable to comment on vestibular recruitment at this time for the same reason.

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A national symposium entitled "Health Policy and Chronic Illness: The National Debate" will be held February 17-18, 1979 in San Francisco. This symposium is sponsored by the University of California, San Francisco Schools of Medicine, Nursing, Dentistry and Pharmacy, Continuing Education in Health Sciences, the Health Policy Program and the Multipurpose Arthritis Center. For information call: (415) 666-3904. For registration call: (415) 666-2894.

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COMPUTERIZED SCREENING OF THE HUMAN VESTIBULOSPINAL SYSTEM

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The vestibular nerve projects rostrally via the ascending medial longitudinal fasiculus (MLF) to eventually supply the ocular muscles and also projects caudally via the descending MLF to eventually supply the spinal and limb musculature. Electronystagmographic techniques are designed to evaluate only portions of the vestibulo-ocular and oculomotor systems. Vestibular lesions affecting only the caudal vestibular nerve distributions or lesions affecting both neural distributions, therefore, cannot be objectively assessed except for the vestibulo-ocular component. A promising recording technique for the evaluation of the vestibulospinal system has been developed and tested in the Raymond E. Jordan Human Vestibular Systems Laboratory. A comparison of two data analysis techniques in normal subjects, unilateral vestibular lesion patients and patients with unilateral lesions of the cerebellar hemispheres have provided pilot data which indicate that the vestibulospinal stability test technique holds considerable promise for both research and clinical evaluation of the human vestibulospinal system.

Objective and quantitative methods for assessment of an organ system status have become increasingly important in virtually all specialties of clinical medicine. The important contributions of objective audiometric techniques such as brain stem evoked potential recordings to clinical diagnosis are well-known to otologists. Audiometry has developed far more rapidly than vestibular system assessment methods, and most of the advances in vestibular testing have been limited to vestibulo-ocular system tests. A method of quantitating human stability characteristics for localization of dysequilibrium disorders affecting the vestibulospinal system was developed in our laboratories.[1] Data from three well-documented groups of patients selected from over 5,000 patient recordings, have been carefully analyzed for the most reliable parameter deviations from normal response limits.

METHODS AND MATERIALS

APPARATUS

The apparatus has been previously described.[1] Since that report, the vestibulospinal stability test (VESST) system has been significantly improved. First, a smaller microcomputer system (LSI-11) was interfaced with the platform amplifiers, graphics terminal and hard copy unit. The slower LSI-11 system may be operated independently of the hierarchically programmed PDP11/40 minicomputer which frees the larger computer for other, simultaneously performed, vestibular system laboratory tests. Alternatively, the faster and larger PDP11/40 may be used to analyze and copy the VESST, if desired. This configuration permits uninterrupted use of the posturography test system, while optimizing reporting of results.

All coordinates were referenced according to the standards suggested by Hixson et al[2]

SUMMARY OF TEST PROCEDURE

Instructions given to the subject were identical to those used to obtain an unrecorded Romberg test in the clinic, as follows: After removing shoes, the subject was instructed to stand with knees locked on the force platform in the standard (feet together) or tandem (heel-to-toe, dominant foot behind) foot positions, with eyes open or closed. Four maneuvers were recorded: 1) feet together, eyes open; 2) feet together, eyes closed; 3) feet heel-to-toe, eyes open; and 4) feet heel-to-

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From the Department of Otolaryngology, University of Pittsburgh School of Medicine, and the Raymond E. Jordan Human Vestibular Clinical Testing Laboratory at the Eye and Ear Hospital, Pittsburgh, Pennsylvania. This project supported by grants from the Martha Edwards Lazear Foundation, George H. and Margaret McClintic Love Foundation, Richard King Mellon Foundation, The Deafness Research Foundation and the United States Department of Health, Education and Welfare, Public Health Service, National Institutes of Health, No. NS13286.

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toe, eyes closed. During each maneuver the subject was asked to perform the Jendrassik maneuver by hooking his hands by the fingers and laterally extending his arms in tension in order to reduce articulated pelvic, upper torso and head sway. In this manner, the patient approximated a nonarticulated, oscillating inverted pendulum. Each subject was tested using two 15-second trials per maneuver. Continuous display of center-of-force calculations throughout the testing procedure on the computer display enabled the technician to properly position the subject before each trial was recorded.

PATIENT GROUPS

Fourteen patients who satisfied the AAOO criteria[3] for unilateral Ménière's disease were selected as subjects afflicted with a peripheral (intralabyrinthine) vestibular lesion. Six subjects with surgically confirmed acoustic neuromas limited to the internal auditory canal (and without brain stem compression) were chosen to represent an anatomical "first-order" vestibular afferent nerve lesion group. Another six subjects with surgically confirmed unilateral lesions of a cerebellar hemisphere were chosen to represent an abnormal "central" neuromuscular control system group. Postural center-of-force characteristics of these patients were compared with the performance of at least ten age-matched normal subjects per age decade.

DATA ANALYSES PERFORMED

1. Root mean square (RMS) calculations of Cartesian center-of-force (x,y) displacements: The average value for each 15-second time series was calculated and then subtracted from the data in order to correct for the offset of the subject from the center of the platform. Next, the RMS value of this zero mean data was calculated.

2. Velocity of the Cartesian center-of-force coordinates was approximated by taking the scaled first difference of the displacement data. Next, the RMS value of the velocity was calculated as described above.

3. The power spectral density (PSD) of the x,y, and r center-of-force coordinates was calculated using fast Fourier transform (FFT) techniques.[4] The information regarding the actual frequency content of the PSD plots will be the subject of another report. For this report, an estimate of the energy expended for postural control was obtained by integrating the PSD plot.

RESULTS

Cartesian coordinate, polar coordinate and position or velocity plots as a function of time have been studied by many previous investigators, especially in Europe.[1] These data provide important qualitative information about a subject's upright postural control and will be presented in a more thorough review of the subject.* For this report, only the phase plane and PSD integral data were compared.

PHASE PLANE CALCULATIONS

Standard Romberg (SR) Positions (Fig. 1).

EYES OPEN (EO) (Fig. 1A, B). With visual orientation permitted, many of the patients over age 30 fell outside two standard deviations regardless of lesion location. Under the age of 30, only the subjects with central lesions consistently fell outside normal ranges.

Displacement (Fig. 1A) and velocity plots (Fig. 1B) were equally effective in detecting abnormalities, regardless of lesion site. One child with a cerebellar hemangioma and two older subjects with acoustic neuromas demonstrated relatively larger shifts outside normal ranges on velocity plots in comparison with displacement measures.

EYES CLOSED (EC) (Fig. 1C, D). Displacement plots (Fig. 1C) demonstrate about the same distribution for most subjects as described for eyes open performance with a tendency for some subjects with acoustic neuromas and cerebellar lesions to markedly increase their displacement amplitudes. One acoustic neuroma subject stepped off the platform in order to prevent a fall.

Standard Romberg eyes closed velocity plots (Fig. 1D) (SREC) demonstrate a marked increase in normal limits in comparison with the standard Romberg eyes open (SREO) trials. A marked shift out of normal ranges occurred for most subjects over 30 years of age.

The velocity plots from one child with a cerebellar lesion showed much larger deviations from normal than displacement measures (Fig. 1C, D). An interesting tendency was observed in

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*Black FO: The assessment of human vestibulospinal function: theoretical and clinical application, 1978, in preparation.

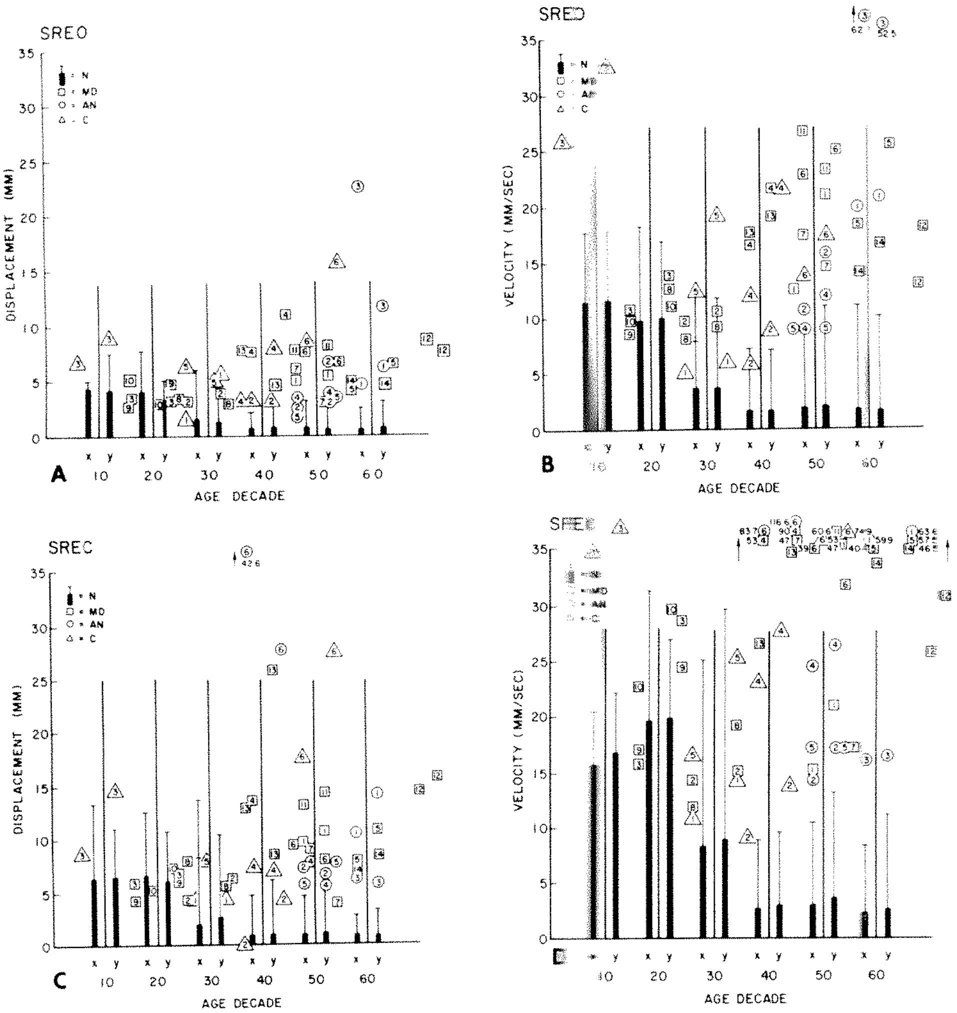

Fig. 1. Displacement (A, C) and velocity (B, D) values for the standard Romberg (SR) series. A, B) Standard Romberg, eyes open (SREO) series. C, D) Standard Romberg, eyes closed (SREC) series. Upper age of decade and recording axis appear along abscissa. Error bars display normal ranges (means and two standard deviations). Ménière's disorder (MD), acoustic neuroma (AN) and cerebellar hemisphere lesion (C) patient data are displayed as shown. The number inside each symbol is a patient identification code. These ordinates and data points are employed for Figs. 1 and 2. A, B) With eyes open, many of the younger patients fall within normal ranges. As age increases, displacement amplitude increases and velocity control diminishes in patient populations as compared to normal. C, D) Upon removal of visual cues, displacement tends to increase to a greater degree in older subjects with central disorders and acoustic neuromas. Velocity control diminishes in both normal and abnormal subjects but to a significantly greater degree in older patients.

some normal subjects* which appeared to be exaggerated in abnormal subjects. On phase plane plots, some normal subjects aged 30 and younger, were more unstable (larger displacements and velocities) in the x (anterior-posterior) than in the (side-to-side) y axis. Patients over the age of 30, on the other

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*Unpublished observations.

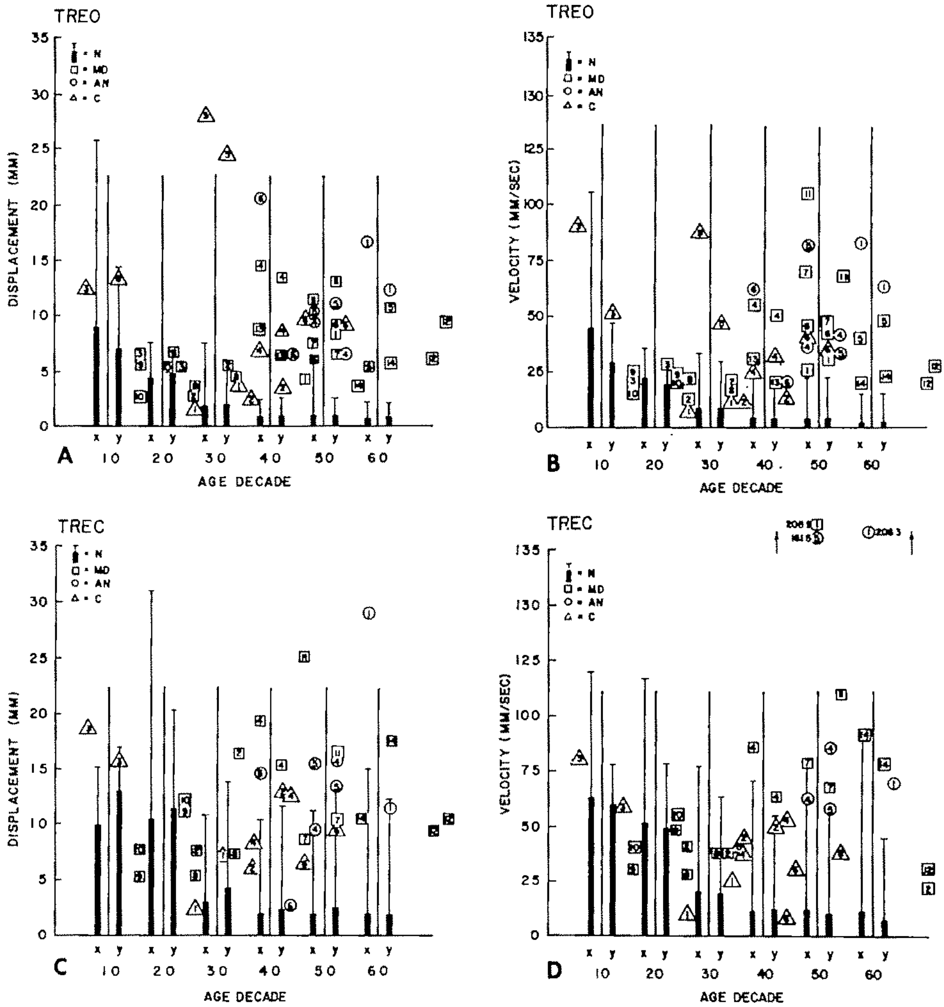

Fig. 2. A, B) For the tandem Romberg, eyes open (TREO) trials, the more unstable condition tends to show similar deviations from normal as shown for the SR trials. (Note scale change for velocity.) C, D) For those subjects who could perform the TREC trials, loss of velocity control, especially in the older age groups appeared to be the more sensitive indicator of abnormality.

hand, tended to demonstrate relatively more unstability along the y as compared to the x axis.

In abnormal subjects, the ratio of displacement (D) to velocity (V) decreased markedly in subjects over age 30 and dropped below unity in our group of abnormal children. Typical normal ratios are shown in Table 1.

Tandem Romberg (TR) Positions (Fig. 2).

EYES OPEN (Fig. 2A, B). Displacement plots (Fig. 2A) demonstrate approximately the same performance as for the more stable SR position for most subjects. One third-decade subject with a cerebellar hemisphere lesion and one fourth-decade acoustic neuroma subject performed well outside normal limits in the more unstable TR position in comparison with displacements recorded during the SR position.

Velocity plots (Fig. 2B) for the most part, demonstrated the same relative

TABLE 1. TYPICAL RMS DISPLACEMENT-TO-VELOCITY RATIOS IN MIDDLE-AGED NORMAL SUBJECTS

	EO	*EC*
SR	1:2	1:3
TR	1:5	1:7.5

Ratios vary as a function of age.
RMS - Root mean square; SR - Standard Romberg; TR - Tandem Romberg; EO - Eyes open; EC - Eyes closed.

normal vs abnormal relationships as demonstrated for the SR positions.

EYES CLOSED (Fig. 2C, D). Many subjects, especially those with central lesions and older subjects with vestibular lesions could not perform this test. For those subjects who could perform the test, roughly the same distribution of normal vs abnormal was present as for the SREC displacement and velocity plots.

INTEGRATED POWER SPECTRA

Because of the differences in stability recorded on the phase plane plots along the x and y axes, from age to age and group to group, all data were converted to polar vectors for power spectral analyses. The calculated power spectral integrals (PSI) therefore reflect fluctuations in polar vector amplitudes.

Standard Romberg Position.

EYES OPEN. The integrated power spectra for the SREO trials (means and one standard deviation for both the Ménière's disease and acoustic neuroma groups) overlapped with normal data. A much greater variation was recorded from the Ménière's disease group (Fig. 3). There was a minimal overlap of the posterior fossa (central) lesion group with normal range, however, there were no significant differences between energy expended by the abnormal group for the SREO series.

EYES CLOSED. Upon visual deprivation, both normal and abnormal groups significantly increased energy expenditure relative to values derived with EO. There was much less overlap between normal and abnormal ranges and relatively less overlap between "central" and "peripheral" lesion groups (note scale change in Fig. 3). Performance of the Ménière's disorder and acoustic neuroma groups was virtually identical but both groups performed well outside normal ranges (re: mean and upper standard deviation). The posterior fossa lesion group performed with a markedly increased variation which overlapped in the lower ranges with Ménière's disorder and acoustic neuroma groups. For the SR position, the greatest variation occurred in the Ménière's disease group with EO, and in the posterior fossa group with EC.

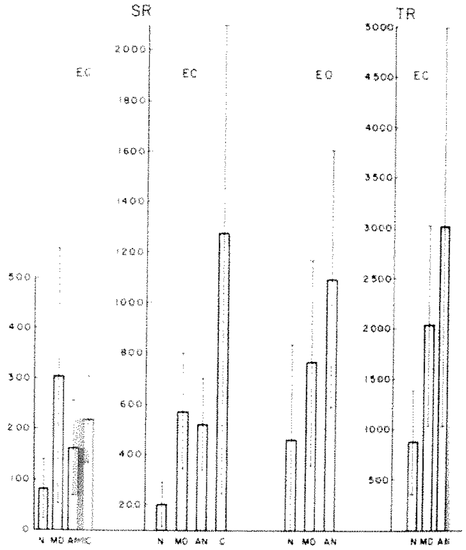

Fig. 3. Ordinates - Power spectral integrals in arbitrary units. SR and TR - Standard and tandem Romberg respectively. Other abbreviations as previously noted. Bars represent mean; error limits represent one standard deviation. Several cerebellar lesion patients required support in TR positions, therefore data were not plotted. Discussion in text.

TANDEM ROMBERG POSITION EYES OPEN. Energy expenditure during the more unstable TREO maneuvers corresponded in magnitude with the SREC trials, but with greater variance in the TR position. There was also considerable overlap in the performance of all groups, normal and abnormal, in the more unstable TREO series.

EYES CLOSED. Integrated power spectra means and standard deviations overlap considerably between normal and posterior fossa lesion groups but to a lesser extent with the Ménière's disease and acoustic neuroma groups. (Note second scale change in Fig. 3.) Except for the central lesion group, the relative increase in energy expenditure from EO to EC test conditions was approximately the same for both SR and TR maneuvers. All of the subjects with cerebellar lesions required support in order to perform TR positions with eyes closed.

POWER SPECTRAL INTEGRAL RATIO CALCULATIONS

Relative Energy Expenditure With and Without Visual Orientation (△E). Integrated power spectral plots may be considered estimates of energy expenditure. However, the ratio between the EO to the ECPSI did not change significantly (Fig. 4). Systematic changes in the integrated power spectra from maneuver to maneuver and trial to trial may be summarized by computing the energy difference between the EC and EO trials divided by energy from the EO trial as follows:

$$\triangle E = \frac{E \text{ closed} - E \text{ open}}{E \text{ open}}$$

Where: $\triangle E$ = relative energy change between trials

E = power spectrum integral

If, on the other hand, a ratio of SR to TR △E values were compared, significant differences in group performances could be observed. Most of the acoustic neuroma and the posterior fossa lesion subjects fell outside normal ratio △E ranges. Five well-compensated or quiescent Ménière's disease patients fell within normal ratio △E limits (Fig. 4). All of the six posterior fossa lesion patients fell well outside normal ranges ($P = 0.05$). The mean response for the central lesion group was approximately 15 times the normal group mean. Responses from most of the remaining patient groups who could perform the maneuver were widely distributed relative to normal with four "inactive" Ménière's disorder patients recording within normal limits.

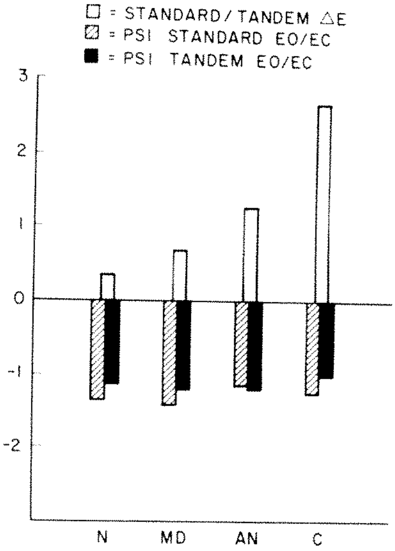

Fig. 4. Period averaged power spectral integral (PSI) eyes open (EO) to eyes closed (EC) ratios (lower half of figure). There were no significant differences between groups, which implies that the *relative* effect of visual orientation upon posture control was the same in all groups. However, when the ratio of SR to TR △E was compared, significant differences between groups were identified.

DISCUSSION

PHASE PLANE PLOTS

Using a simplified mechanical model, a human standing in one of the Romberg positions may be viewed as an inverted pendulum with movements described by equations of oscillatory motions. If a pendulum swings at a constant amplitude and frequency, plots of the pendulum head position along the abscissa and pendular head velocity along the ordinate will, if scaled properly, describe a circle or ellipse. If the amplitude decays without a change in frequency, an enclosed spiral plot will result; if the amplitude increases, conditions otherwise unchanged, an open spiral plot will result. Because the standing human is constantly oscillating, a stable subject will superimpose over time many combinations of plots consisting of combinations of near circles, ellipses or closed spirals. Unstable subjects will, on the other hand, describe combinations of circular and open spiral plots.[4] In the first case, increasingly stable plots will yield progressively greater root-mean-square displacement to velocity ratios. In the latter case (increasing instability) RMS D/V will yield progressively decreasing ratios.

Patients with peripheral or VIII nerve lesions will demonstrate progressively larger RMS velocity as compared to displacement as they perform increasingly difficult Romberg maneuvers. The D/V will therefore decrease progressively from maneuver to maneuver. The greatest shifts occur in the older age groups who tend to fall well outside two standard deviations for both D and V values above the age of 30.

Four of the six patients with cerebellar disturbances demonstrated markedly increased V values, even in the SR positions. Their D:V ratios were approximately 1:5 and 1:7 with EC and EO trials respectively. Tandem Romberg performance was highly variable (two could not perform the task and another required support). The subjects who could perform the task unsupported yielded the lowest D/V (1:10) recorded.

The phase plane plots clearly demonstrate that the measured V control of body movements deteriorates to progressively greater degrees in normal subjects, with Ménière's disease and acoustic neuromas patients, and patients with cerebellar hemisphere lesions as they perform the Romberg test series. Displacement values show similar but not as dramatic increases.

POWER SPECTRAL ANALYSIS

In our opinion, polar vector coordinate fluctuations of the patient's center-of-mass more accurately reflect a subject's energy expenditure, particularly if both normal and abnormal data are to be compared. The data presented here represent the first step toward an attempt to determine which force vectors (r, x and y) are significantly altered by various types of equilibrium disturbances. Power spectrum integral data were averaged for each group, which accounted for the relatively large variances observed in the abnormal groups.

The SR and TR test series appears to present the extremes from the most to the least stable upright stance conditions respectively. Preliminary analysis of postural control in normal and abnormal subjects suggests that the SR provides too much stability (except, perhaps for patients with central nervous system disorders) on the one hand while the TR provides too little stability for the many unsteady subjects on the other. The data presented support the concept of force platform Romberg test recordings as a method of screening the integrity of the vestibulospinal system, however, a test paradigm more difficult than the SR but less difficult than the TR must be developed in order to identify with more certainty peripheral vestibular, oculomotor and other central nervous system disorders which result in disrupted motor control. Such a test would provide the otologist and neurologist with a far more valuable diagnostic test of the vestibulospinal control system. Other possible approaches include earlier screening for postural control disturbances. How reliable and sensitive the Romberg test series would be in subjects who have not lost redundant mechanisms for postural control remains to be determined.

The concept of a vestibulospinal test which records information transfer as coupled from a subject's feet to his supporting base appears to offer certain advantages over more indirect measurements. Estimates of the forces opposing the feet against a platform, including their trajectory characteristics, time series analysis and energy expenditure estimates, have provided preliminary data in support of force platform recordings as a potentially efficient and quantitative clinical and research method for study of human upright posture control. These relationships will require continued study of a larger patient population before more exclusive quantitative characteristics of normal and abnormal postural control characteristics can be described. However, ratio comparisons, particularly those derived from phase plane and integrated power spectra, suggest that the difference ratios between EO and EC trials may yield relatively sensitive predictors of various types of equilibrium control system abnormalities.

CONCLUSIONS

Systematic, and apparently characteristic shifts in the position and V control mechanisms and the energy expenditure required to maintain the Romberg positions occur in both normal and abnormal human subjects. Preliminary data from human upright postural center-of-force measures suggest several potentially fruitful approaches to the study of human vestibulospinal and musculoskeletal control systems in normal and abnormal subjects. Careful analysis of the stability characteristics as reflected in center-of-force recordings appears to hold considerable promise for both clinical and research studies.

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CANADIAN OTOLARYNGOLOGICAL SOCIETY

The annual meeting of the Canadian Otolaryngological Society will be held June 6-8, 1979 at the Harbour Castle Hotel, Toronto, Ontario. Inquiries may be sent to Dr. David Briant, Secretary, St. Michaels Hospital, Toronto, Ontario M5B 1W8.

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1979 EAR SURGERY COURSE

Four day intensive ear surgery course will be given January 28-February 1, 1979 in Tampa, Florida. For details write: Southern Foundation OBH, % J. Brown Farrior, MD, 509 Bay Street, Tampa, FL 33606.

Ann Otol 87:1978

VESTIBULAR RESPONSES TO BITHERMAL CALORIC AND HARMONIC ACCELERATION

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Vestibulo-oculomotor responses from 33 patients with either peripheral labyrinthine or central pathology were compared using the standardized Fitzgerald-Hallpike bithermal caloric and harmonic accelerations. In numerous cases (40%), patients with normal caloric responses reflected abnormalities in either their phase relationships or labyrinthine preponderance to sinusoidal acceleration. Results clearly indicate that harmonic acceleration provides additional information to the clinician in the evaluation of vestibulo-oculomotor pathology that is not reflected in the responses to standard caloric tests.

In recent years an increased interest among researchers and clinicians in the use of harmonic (sinusoidal) acceleration in the evaluation of vestibular function has been mainly predicated on the increased sophistication and availability of torque motor-driven systems and minicomputers. There are a number of methods of generating the input stimulus and evaluating the eye movement output;[1-3] basically, they all have as their goal the describing of input-output relationships.

We have been using pure sinusoidal stimulation for the past ten years in studies of cerebellar-vestibular relationships[4,5] and were impressed with the apparent repeatability of responses to this type of acceleration. More recently, we have been studying the usefulness of this stimulus in the evaluation of peripheral and central vestibular pathology.[6,7] One important consideration is the relationship between responses to conventional caloric stimulation and those to harmonic acceleration. The present study was designed to compare these two forms of stimulation in a clinical population; only those patients with well-defined symptoms were used as subjects.

METHODS AND MATERIALS

Thirty-three clinical patients were selected from a population referred to the Otolaryngology Service at Wilford Hall USAF Medical Center. All patients with peripheral vestibular pathology were selected and referred by a neurotologist. Each patient was given the same series of tests consisting of pursuit tracking, optokinetic stimulation, tests for spontaneous and positional nystagmus, bithermal caloric stimulation, and harmonic accelerations. The caloric test consisted of 250 cc of water delivered over a 40-second period at temperatures of 30 C and 44 C. All recordings were made in reduced red light illumination with the patient's eyes closed except for a ten-second period in which the subject was tested for fixation suppression. Mental arithmetic and questions were used to maintain the subject's arousal level. A five-minute interval was employed between each stimulus. Eye movements were recorded by conventional electrooculographic (EOG) techniques, amplified with a three-second time constant, and written out on a Beckman dynograph recorder. Records were obtained for the summated horizontal and for the left and right eyes; vertical movements were recorded from the right eye only. Each caloric record was hand-scored by the same technician, by taking an average of the slow-phase velocity for ten nystagmic beats during the period of maximum response. These measures

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The research reported in this paper was conducted by personnel of the Clinical Sciences and Biometrics Divisions, USAF School of Aerospace Medicine, Aerospace Medical Division, AFSC, Brooks AFB, Texas; and the Otolaryngology and Neurosurgery Services, Wilford Hall USAF Medical Center, Aerospace Medical Division, AFSC, Lackland AFB, Texas. The voluntary informed consent of subjects used in this research was obtained in accordance with AFR 80-33.

Presented at the meeting of the American Otological Society, Inc., Palm Beach, Florida, April 23-24, 1978.

TABLE 1. RESPONSES TO CALORIC STIMULATION

Ménière's N=18

44% within normal limits
$\bar{x}$ UW = 12.0% S.D. = 10.3%
$\bar{x}$ DP = 9.0% S.D. = 7.9%

Neuromas N=4

25% within normal limits
$\bar{x}$ UW = 19.5% S.D. = 8.3%
$\bar{x}$ DP = 8.0% S.D. = 5.8%

Central Lesions N=11

18% within normal limits
$\bar{x}$ UW = 22.8% S.D. = 23.0%
$\bar{x}$ DP = 26.4% S.D. = 32.3%

were then converted to percentages of unilateral weakness and directional preponderance according to the method of Jongkees and Philipszoon.[8]

Harmonic acceleration was generated by a torque-motor turntable system.* The subject was seated in a chair which was completely encapsulated by a lightweight metal drum. The head was positioned and supported by a headrest so as to place the horizontal canals in the plane of rotation. All trials were conducted with the subject's eyes open in the dark. Again, mental arithmetic and questions were used to maintain arousal and there was a five-minute interval between trials. The EOG was obtained for the summated horizontal and the left and right eyes independently.

Each patient was tested at frequencies of .01, .02, .04, .08, and .16 Hz at a maximum velocity of 50°/second. The resulting accelerations varied from 3°/sec^2 at .01 Hz to a maximum of 50°/sec^2 at .16 Hz. Data were analyzed by methods which have previously been described in detail.[1] The output measures of interest were the phase relationships between the input stimulus and the eye movements, the gain of the response, and labyrinthine preponderance.

The phase lag with reference to the input acceleration was obtained by cross-correlating the tachometer input signal with the inverted slow-phase derivative and then subtracting 90° from this result.[1] Gain was measured by taking the ratio of the peak input velocity to the peak slow-phase eye velocity. Labyrinthine preponderance was determined by separately integrating the total slow phase output to the left and to the right and then converting the result to percentages. These response measures were obtained for each frequency tested. Data from the clinical patients were compared to responses from 50 normal subjects from a previous study.[7]

The group with peripheral vestibular involvement consisted of 18 patients with Ménière's disease; in each case the history conformed with criteria proposed by the Committee on Hearing and Equilibrium of the AAOO.[9] These patients ranged in age from 14 to 59 years with a mean age of 38 years and a standard deviation of 14 years.

The group with central abnormalities consisted of 15 patients with the following diagnoses: brain stem infarction, 2; multiple sclerosis, 2; cerebellar degeneration, 2; head trauma, 4; basilar artery aneurysm, 1; and acoustic neuroma, 4. We are aware that many authorities consider "peripheral" to mean all structures from the brain stem to the end-organ; however, all four of these patients had tumors which contacted either the brain stem or cerebellum and have therefore been included in the central category. The four neuroma patients were 31, 37, 44, and 56 years of age. The other central patients had a mean age of 41 and a standard deviation of 14 years, ranging from 21-60 years old.

There was also essentially a third category, since seven of the patients with Ménière's disease were tested before and after endolymphatic shunt procedures. In addition, the four patients with VIII nerve tumors were tested before and after surgery. In these subgroups, posttesting did not include caloric stimulation but was limited to only tracking and rotational testing.

RESULTS

Although each patient's data was unique, we felt it would be worthwhile to group their vestibular responses in order to evaluate any overall trend in the data. A detailed study of the pursuit tracking of these patients is the subject of another report.[10] Overall, 33% of the patients tested had caloric responses that were within normal limits; i.e., a directional preponderance or unilateral weakness of less than 20%. Table 1 indicates the percentages for the various groups. As one would expect, as the severity of the symptoms increased so did the percentage of abnormal responses to caloric stimulation.

Vestibular responses to harmonic acceleration also showed decrements that were related to the particular pathology. By categorizing the patients into groups

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*Contraves-Goerz DP-300.

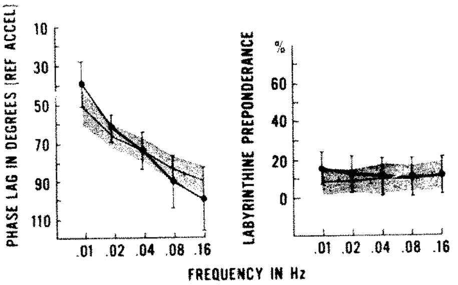

Fig. 1. Means and ±1 standard deviation for 18 patients with Ménière's disease: shaded area and thin line denote data from 50 normals. Note that patients show less phase lag at lower frequencies and a lead above .04 Hz.

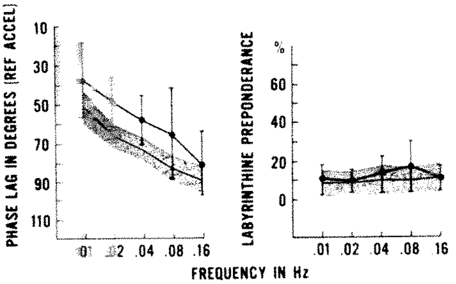

Fig. 3. Means and ±1 standard deviation for 11 patients with central lesions as compared to normals (shaded region). Phase lag at .02 and .08 Hz is over 2 S.D. from the normal means.

(Figs. 1, 2, 3) different patterns were revealed, mainly in their phase shifts. The labyrinthine preponderance (left-right asymmetry) generally was within one standard deviation of the normal means except for the postsurgery neuroma group. Those patients diagnosed as having Ménière's disease displayed a decreased phase lag below .04 Hz, at which point they crossed over the normal means and responded with an increased lag in their oculomotor responses. The four patients with neuromas showed less of a lag than normals at all of the frequencies tested. Following tumor removal by a translabyrinthine approach, they showed a marked increase in asymmetry and a decrease in phase lags that were almost two standard deviations from the normal means. Again, those patients with central pathology showed considerably less phase lag than any of the other groups (excepting, of course, the unilateral labyrinthectomies), and differed considerably from the normal subjects.

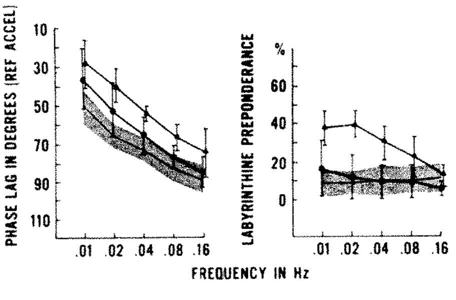

Fig. 2. Means and ±1 standard deviation for 4 neuroma patients before and after surgery. Patients show less lag at all frequencies; following surgery they show marked decrements in both phase and labyrinthine preponderence. •——• - Presurgery. ▲——▲ - Postsurgery.

CASE REPORTS

Case 1. A 44-year-old male had noted a slowly progressive hearing loss in his right ear for five years. He requested an evaluation in the summer of 1977. He had no history of dizziness but reported occasional mild unsteadiness. Tinnitus began in the right ear in 1976. The physical examination showed the Weber lateralizing to the left. The audiogram showed a right sensorineural loss with a pure-tone average (PTA) of 42 dB; the speech reception threshold (SRT) was 40 dB. Speech discrimination was 52% on the right. The left ear was normal. Brain stem audiometry showed a 0.7 msec delay of the right wave V (normal latency <.5 msec) when compared to the left. Internal auditory meatus views showed flaring of the right canal. Computerized tomography (CT) scan was normal, but his posterior fossa myelogram showed a 1½ to 2 cm cerebellopontine angle mass. In October 1977, a 2½ cm acoustic neuroma was removed by a translabyrinthine approach. The tumor was firmly attached to the brain stem just below the rootlets of the V cranial nerve; it indented the pons and was very adherent to it but did not appear to be compressing the cerebellum. Postoperatively, the patient had moderate vertigo but was returned to full duty after a three-week period of recuperation. Figure 4 shows pre- and postsurgical data from this patient. The caloric test indicated a unilateral weakness on the right side. Rotational testing indicated a labyrinthine preponderance to the left which was greatest at .01 Hz. The phase shifts were normal at the higher frequencies; however, .02 and .01 Hz indicated a minimal decrement from the normal values. He was again tested 15 days after surgery and had a labyrinthine preponderance to the left that was

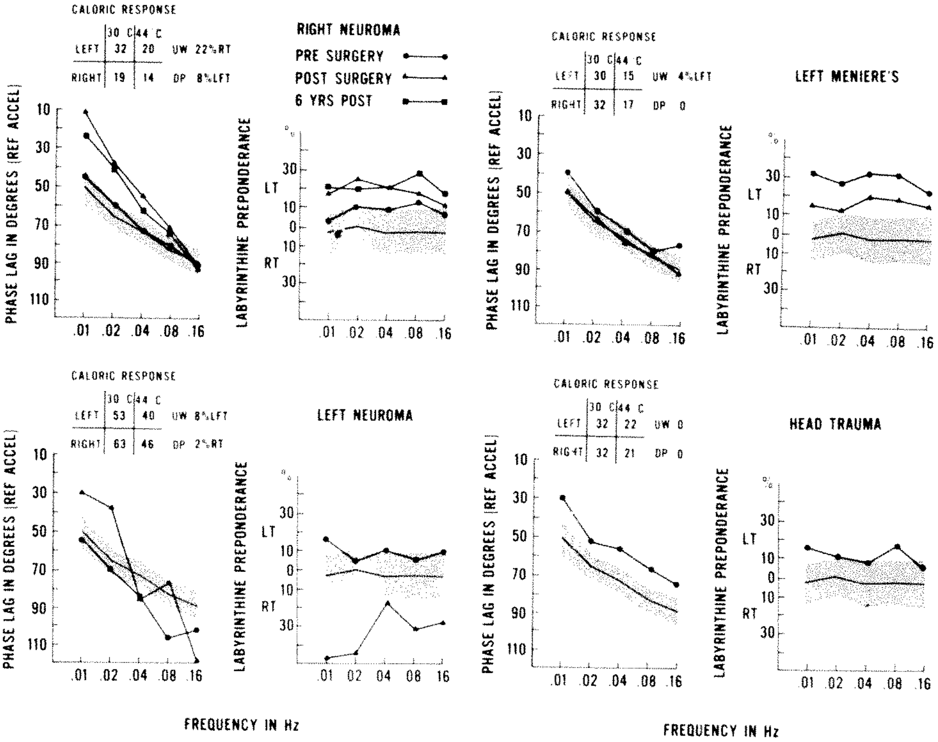

Fig. 4. Comparisons of caloric stimulation and harmonic acceleration responses in four patients with either peripheral or central pathology. • - Presurgery, ▲ - Postsurgery.

greatest (32%) at the lowest frequency and phase shifts that were over two standard deviations from the normal means at the lower frequencies. When retested 35 days postoperatively, he showed some decrease in his preponderance at the midrange frequencies; but his phase shifts had improved by only 5°. Fortunately, we were able to again retest this patient five months postoperatively. His responses at the midrange of frequencies (.02, .04, and .08 Hz) were practically identical to his data at 35 days after surgery. Labyrinthine preponderance was reduced to .01 Hz; however, his phase shift at this frequency was similar to his first postoperative test. The only improvement in his responses to acceleration was at the highest frequency of stimulation (.16 Hz) where he had returned to within normal limits. When compared to a patient who had a labyrinthectomy six years ago (Fig. 4, right neuroma), it is doubtful that he will regain further compensation to harmonic stimulation.

Case 2. A 31-year-old male noted the onset of a gradually progressive left hearing loss three years prior to admission. In the fall of 1977, he was referred for evaluation. He had no history of vertigo, tinnitus, fullness, or other ear or neurologic symptoms. He was found to have an SRT of 40 dB, a discrimination of 40% on the left, and normal hearing on the right. The acoustic reflex was absent when the stimulus was placed in the left ear. Brain stem audiometry showed an absence of wave V on the left. Petrous apex x-rays showed a widening of the internal auditory canal on the left. CT scan was negative, and a posterior fossa myelogram demonstrated a 1½ to 2 cm smooth cerebellopontine angle mass. In January 1978, a 2 cm acoustic neuroma was removed by a translabyrinthine approach. The tumor was mildly adherent to the facial nerve and cerebellum but did not appear to be pressing on the brain stem. This patient had no postoperative complications. Although he had an extremely high slow-phase velocity in response to caloric stimulation, his data indicated a left unilateral weakness of 8% and a left directional preponderance of 2% (well within normal limits). His data in response to rotational stimulation showed a slight asymmetry with a directional preponderance to the left which was greatest at .01 Hz. However, his phase shifts showed a progressive lead up to .08 Hz at which point they were over two standard deviations from the normal values; at .16 Hz he showed less of a lead but was still outside the normal range. The patient was retested 11 days following surgery and showed a marked preponderance (45%) at the two lowest frequencies, which decreased at .04 Hz and then increased again at the higher frequencies. His phase shifts were characteristic of a labyrinthectomized individual, with the exception of .04 Hz which showed no change and .16 Hz where he now had a marked lead in his vestibular response (Fig. 4, left neuroma). This patient's data appeared to show an interaction between peripheral labyrinthine defects (low-frequency decrements) and central brain stem involvement (high-frequency decrements). This finding was substantiated by data from his pursuit tracking which showed left eye tracking impairments before surgery which were increased by the surgical procedure.

Case 3. A 38-year-old male had a 2½-year history of inner ear symptoms. His initial symptoms began with fullness and tinnitus in the left ear. Four months later he had his first vertiginous attack lasting approximately one hour. He felt weak and nauseated for the rest of the day. Since that time, he has had two types of attacks. The classic Ménière's attacks occurred about once a month and included a roaring tinnitus, fullness in the left ear, spinning vertigo, nausea, and a decrease in hearing. Occasionally he would vomit. He usually felt nauseated for about 18-24 hours postattack. The second type of attack occurred one to two times a week and consisted of increased tinnitus on the left, fullness, and a mild unsteadiness; these attacks lasted 10-30 minutes. In the summer of 1976, he had an evaluation consisting of audiogram, electronystagmogram (ENG), CBC, T_3, T_4, triglycerides, cholesterol, FTA-ABS, and 2-hour postprandial blood sugar. The audiogram and ENG were consistent with Ménière's disease. All other studies were negative. He was placed on diuretics, Valium®, and Pro-Banthine®. There were no changes in his symptoms. In the fall of 1977, he was referred for consideration for surgery. His previous workup was repeated, including a 2-hour glucose tolerance test (GTT) which was normal. A detailed allergy history was negative. However, the glycerol test was positive.[11] In February 1978 a left endolymphatic mastoid shunt was accomplished.[12] The sac was easily identified but was quite fibrotic and thickened. The patient had no postoperative problems. He has been symptom-free, on no medications, since the operation but at present is only two months postoperative. This patient was given both caloric and rotational tests one week before the shunt procedure. His caloric responses were almost perfectly symmetrical and were computed at a 4% unilateral weakness on the left with 0% directional preponderance. The warm stimuli produced less response than the cold, but this effect was bilateral. However, he showed marked asymmetry (average of 30%) in his slow-phase output in response to sinusoidal acceleration; this was fairly flat across all frequencies tested. The phase relationships of his eye movements to the input stimulus indicated a deviation from normal values at .01 and .16 Hz. This patient was evaluated one week postsurgically at which time he showed a reduction in his asymmetry which was greatest at .01 Hz. The overall shape of his labyrinthine preponderance was almost identical to his preshunt data; however, he showed an overall reduction in asymmetry which was greatest (20%) at the two lowest frequencies. His phase relationships showed a dramatic improvement and were close to the normal means at all frequencies tested (Fig. 4, left Ménière's).

Case 4. A 41-year-old female suffered head trauma to the left parietal-temporal region in an automobile accident (March 1977) and was unconscious for approximately two minutes. She was dizzy for some time afterwards but could function fairly well. By the fall of 1977 she had headaches and mild dizziness associated with rapid turning of the head. In January 1978 she was evaluated for persistent headaches and dizziness. There were no other symptoms and the neurological examination was normal. The workup, including EEG and CT scan, was normal. The final diagnosis by the neurologist was tension headaches and she was referred for otologic evaluation. All studies, including hearing and caloric testing, were completely normal. As shown in Figure 4 (head trauma), she had a symmetrical response to caloric irrigation; however, her responses to harmonic acceleration showed phase shifts that were almost two standard deviations from the normal mean at all frequencies.

DISCUSSION

It is obvious that each patient's data is unique and the results of vestibular testing will vary accordingly. However, it does appear that a number of conclusions can be drawn from the present results. One of the major advantages of using sinusoidal angular acceleration as a stimulus is the repeatability of the phase measures, which is obviously related to the control over the stimulus input and the fact that the semicircular canals are "designed" to precisely resolve angular accelerations into appropriate eye movements. The phase relationships between the input and output also appear to be independent of the intensity of the stimulus (assuming it is above threshold) and are not affected by the arousal level of the subject. However, this does not appear to be true for the gain or total output of the system. In addition, patients can be tested soon after undergoing ear surgery and can, therefore, be evaluated for the effects of the surgical procedure. This capability should eventually allow the surgeon to determine if surgery would be of benefit to the patient and may lead to a better under-

TABLE 2. MAXIMUM SLOW PHASE VELOCITY

	*Normals N=559**			
	30°		*44°*	
Left	x̄ = 24°	S.D. = 12°	x̄ = 20°	S.D. = 11°
Right	x̄ = 23°	S.D. = 10°	x̄ = 21°	S.D. = 11°

*Data collected over a 5-year period: all testing was accomplished with the same equipment and by the same technician. The results were stored in a computer repository for retrieval of data.

standing of what these procedures are doing to the vestibular apparatus. Another obvious advantage of rotational testing is the ability to see if the patient's vestibulo-ocular reflex response is changing; i.e., improving or getting worse. This appears to be mainly true for the phase measures since the labyrinthine preponderance does decrease somewhat following a labyrinthectomy, but there is practically no evidence of compensation for the phase relationships at the lower frequencies.

Unfortunately, the caloric test is easily influenced by one extreme response and even with a repeat test one may not be able to eliminate this factor. We have also found that results from caloric studies vary considerably both within and between various laboratories. Sills et al[13] reported that the warm stimulus produced a greater and more variable response than cold. In a previous study,[14] the senior author of this paper obtained data that indicated the cold stimulus leads to a greater response. However, data from 559 normal subjects would suggest little difference between the two stimuli (Table 2). One is therefore faced with the problem of determining which test agrees with the patient's symptoms and other related findings.

Frequency stimulation can be applied to the vestibular system in a number of ways such as white noise, sum of sinusoids, or single frequencies. There are also a number of advantages of single frequency sinusoids: it is possible to determine if the response is changing phase and amplitude within each cycle; accurate measures of asymmetry can be obtained at each frequency; very low frequencies can be used; and the test is identical for each subject. The major disadvantage of this method is the time (approximately 45 minutes) that it takes to perform the test. However, our data indicate that in some patients the caloric test appears to be similar to testing at frequencies of 0.2-.08 Hz, based on measures of labyrinthine preponderance. In this regard, the standard bithermal caloric test may only be testing a narrow range or portion of the semicircular canal response. Like hearing, the system may function quite well to one or two stimuli and yet have deficits that are not revealed by the caloric stimuli. For example, how diagnostic would an audiogram be if it consisted of only two frequencies and intensities of stimulation? The lowest harmonic frequency (.01 Hz) appears to reveal deficits related to peripheral function which are not revealed by caloric testing, while responses at the higher frequencies show decrements related to central lesions. The fact that some patients show "hyperactive" responses to caloric stimulation, or even in some cases a reversal in preponderance, supports Torok's studies[15] of vestibular recruitment. We found that a number of patients with Ménière's disease showed a marked labyrinthine preponderance during acceleration toward the involved ear. In these cases, it appears that the canals are more sensitive to the input and reflect a type of recruitment.

Considerably more research is required to determine the value of harmonic acceleration as a diagnostic and prognostic test. It does appear that this modality provides the neuro-otologist with quantifiable and repeatable data that are not available from caloric testing, which can aid in the evaluation and treatment of patients with peripheral and central vestibular lesions.

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INTERNATIONAL CONGRESS ON EDUCATION OF THE DEAF

The International Congress on Education of the Deaf will be held in Hamburg, West Germany, August 4-8, 1980. For further information write: German Convention Service, Hamburg Office, Hohe Bleichen 13, D-2000 Hamburg 36.

Ann Otol 87:1978

NOISE-INDUCED HEARING LOSS

A HUMAN TEMPORAL BONE CASE REPORT

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The histopathology of a case of profound hearing loss which seemed to be induced by noise exposure (explosions and drillings in a gold mine) is reported. The patient's only residual hearing was 250 Hz at 90 dB SPL in the right ear. The major histopathological findings were as follows: Bilateral absence or collapse of Corti's organ was observed in the middle and basal turns of the cochlea; however, in the remaining area (approximately 6.0 mm in range in the apical portion of the cochlea) Corti's organ was well-preserved with a moderate loss in number or atrophy of the hair cells. Bilateral marked decrease of the cochlear nerve was noted in the middle and basal turns; however, the nerve was well-preserved in the remaining apical portion (approximately 6.0 mm in range) of the cochlea. These pathological findings were somewhat less severe in the right cochlea than in the left. In general, there was good correlation between the profound hearing loss and the extensive pathological findings in Corti's organ. The residual hearing in the right ear would seem to be explained by the less severe pathological changes found in the apical portion of the right cochlea than in the left cochlea. In addition to noise exposure, other possible etiological factors contributing to this hearing loss are discussed. These include diabetes mellitus and presbycusis.

Noise-induced hearing loss is a well-documented entity in both clinical and experimental observations. Haberman[1] first reported a case of human temporal bone pathology secondary to noise trauma in 1890. Since then, 17 cases (30 temporal bones)[2-5] with audiometric correlation have been reported histopathologically. Among them, 13 cases (18 temporal bones) demonstrated a close correlation between maximum degeneration changes in the hair cells (restricted to the area of the middle third of the basal turn) and a permanent audiometric shift with a 4 kHz notch. Although other cases showed flat or high-tone losses with hair cell loss extending toward the basal end, no case of profound hearing loss with extensive hair cell loss extending to the middle turn has yet been reported.

The purpose of this paper is to report and discuss the histopathological findings in the temporal bones of a gold mine owner with a history of noise exposure and profound hearing loss.

CASE HISTORY

A 59-year-old, Caucasian male was first seen at the ENT Clinic of the University of Colorado Medical Center in December 1959, with a history of a severe bilateral hearing loss and associated tinnitus of 10 years' duration (1949-1959). The patient had been a gold mine owner for 20 years (1939-1959) and had been exposed to excessive amounts of loud noise (dynamite explosions and drillings) during that time. He also stated that he had begun to wear a hearing aid in his right ear in 1955. The left ear was not satisfactory for a hearing aid at that time. In 1959, he retired from mining. Additional past history given by the patient included the following: during his childhood he had had numerous earaches which were treated by puncturing the eardrums. He also had had mumps which were

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accompanied by atrophy of the right testicle. Since 1952, when he was 42 years of age, he had had diabetes mellitus, which had been controlled by an oral agent. Family history showed that two others of the four brothers in his family had worn hearing aids when they reached their seventh decades.

The examination performed when the patient was first seen in 1959 revealed a healed perforation in the left tympanic membrane but otherwise normal findings. An audiogram, however, revealed a severe sensorineural hearing loss, particularly in the high-frequency range in the left ear (Fig. 1). The patient was advised at that time to take lip-reading classes to supplement the use of his hearing aid.

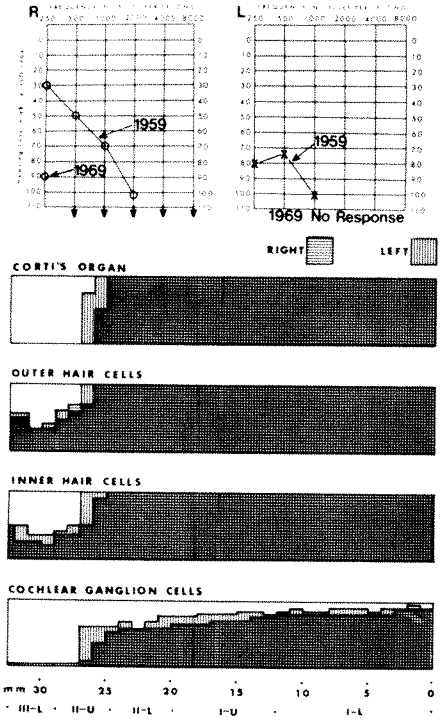

Fig. 1. Audiograms taken in 1959 and 1969 demonstrate patient's severe hearing loss. Barograms show destroyed population of Corti's organ, outer hair cells, inner hair cells, and spiral ganglion cells in both cochleas. The numbers below the barograms indicate the distance in millimeters from the basal end (0 mm). I, II, and III - Basal, middle, and apical turns of the cochlea, respectively. U and L - Upper and lower halves of each of the cochlear turns, respectively.

The patient was followed by the ENT Clinic for ten years, during which time his hearing became progressively worse. An audiogram taken in May 1969, showed that the patient could hear only 250 Hz at 90 dB in his right ear (Fig. 1). The patient died in October 1969, of a myocardial infarction at the age of 69 years. The temporal bones were removed from the refrigerated cadaver, fixed in 10% formalin solution, decalcified, and embedded in celloidin. Serial horizontal sections were cut at 20 μ thicknesses. Every tenth section was stained with H&E and studied under a light microscope.

HISTOPATHOLOGIC FINDINGS

LEFT TEMPORAL BONE

The tissue was well-preserved with minimal postmortem autolysis.

External and Middle Ear. The external ear canal was normal. The tympanic membrane was thin. The structures in the middle ear were essentially normal.

Inner Ear.

COCHLEA. There was a total loss of hair cells, as well as absence of the organ of Corti, in the area 0-27 mm from the basal end of the cochlea (most of the middle turn and all of the basal turn). However, in the remaining area, 27-32.5 mm from the basal end and including the apical portion of the middle turn and the whole of the apical turn, Corti's organ was moderately well-preserved, although a significant number of the hair cells, particularly the outer hair cells, were either missing or atrophic (Fig. 1, barogram). The tectorial membrane was thin and atrophic in all cochlear turns and in some areas of the middle and basal turns the limbus was atrophic and lacked interdental cells. Atrophy of the stria vascularis was seen sporadically in all of the cochlear turns. Reissner's membrane was normal. Both the scala tympani and the scala vestibuli were normal.

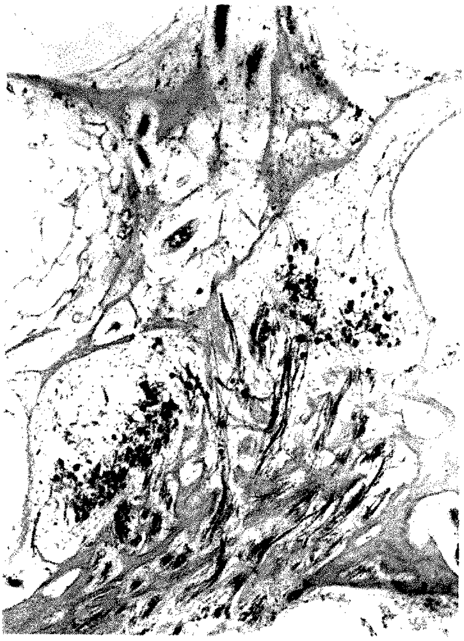

Fig. 2. Left ear. The modiolus of the cochlea demonstrates a severe loss of dendrites, whereas the spiral ganglion cells and the axonal fibers are fairly well-preserved. (H & E, X 90).

Severe loss of the spiral ganglion cells was also observed in Rosenthal's canal in the middle and basal turns (Fig. 1, barogram). In the same area, the dendritic fibers showed more severe decrease in number than the ganglion cells and their axonal nerve fibers (Fig. 2). These findings were more marked in the area innervating the basal turn than in the middle turn. In addition, a cystic structure surrounded by a single, flat epithelial layer of cells was observed in Rosenthal's canal. The inferior cochlear vein and the cochlear aqueduct were normal.

VESTIBULE. All of the vestibular end-organs appeared to be normal with fairly well-preserved hair cells. The crista neglecta was present near the posterior canal crista. Flat epithelial cells were seen in some rugose portions of the endolymphatic sac, surrounded by amorphous collagenous tissues in the subepithelial layer. No other abnormalities were seen in the membranous labyrinth. The vestibular nerves in the cribriform area were normal. The vestibular aqueduct and paravestibular canaliculus were normal.

INTERNAL AUDITORY MEATUS. The axons of the cochlear nerve were moderately atrophic and fewer than normal in number. However, there were no other significant findings in the internal auditory meatus.

RIGHT TEMPORAL BONE

The findings were similar to those described for the left ear.

Inner Ear.

COCHLEA (FIG. 3). Corti's organ was present only as an undifferentiated mass in the area 0-25 mm from the basal end in most of the middle turn and all of the basal turn. There was almost complete hair cell loss (although Corti's organ was identifiable) in the area 25-26 mm from the basal end of the cochlea. In the remaining area, 26-32.5 mm from the basal end (in the apical part of the middle turn and in the entire apical turn) Corti's organ was well-preserved but a moderate number of the hair cells, particularly the outer hair cells, were either absent or atrophic. The tectorial membrane was thin and atrophic in all cochlear turns. Atrophy of the limbus was also observed, accompanied by a decreased population of interdental cells in the middle and basal turns (Fig. 4). Atrophy of the stria vascularis was present sporadically in all of the cochlear turns. Reissner's membrane was attached to the tectorial membrane and limbus in the upper cochlear turns. Both the scala tympani and the scala vestibuli were normal. Severe to moderate loss of the spiral ganglion cells was observed in the area 0-26 mm from the basal end of the cochlea, in the middle and basal turns. Dendritic nerve fibers showed a more severe decrease in number than the ganglion cells and their axonal nerve fibers. The cochlear aqueduct was normal.

VESTIBULE. The vestibular end-organs were normal. No crista neglecta was present in the posterior canal ampulla of this ear. The saccular membrane was

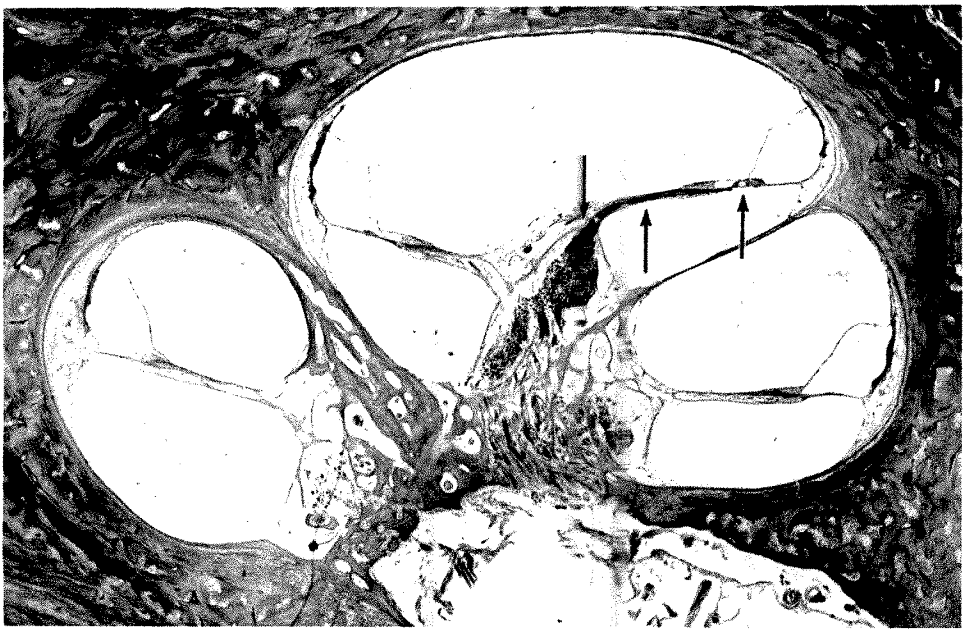

Fig. 3. Right ear. The cochlea demonstrates a total loss of Corti's organ and a moderate loss of the spiral ganglion cells in the middle and basal turns. Note the remaining Corti's organ and nerve fibers in the apical turn (arrows). (H & E, X 24).

collapsed. The ductus reuniens was obstructed. The endolymphatic sac and the vestibular aqueduct were normal.

INTERNAL AUDITORY MEATUS. The findings were the same in the left ear.

DISCUSSION

The major pathological findings observed in this case may be listed as follows: 1) absence or collapse of Corti's organ in most of the middle turn and the entire basal turn of the cochlea on both sides; and 2) a severe decrease in the number of dendritic fibers but with some remaining spiral ganglion cells and axons in the same areas mentioned in 1.

In reviewing the pathological findings as well as the clinical history in this case, we should consider at least three entities as pathoetiological factors: industrial noise trauma, presbycusis, and diabetes mellitus.

To our knowledge, human temporal bone histopathologic study of acoustic trauma with audiometric analysis has been reported in only 17 cases.[2-5] In 1934, Crowe et al[2] reported two cases with histories of noise exposure and high-tone deafness. Histological examination showed degeneration of Corti's organ and the cochlear nerve in the lower basal turn.

In 1964, Igarashi, et al[3] reported two cases of high frequency hearing loss in which the loss was most severe at 4 kHz. They demonstrated degenerative

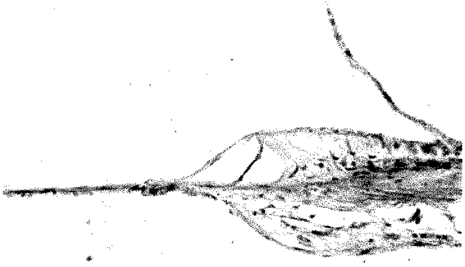

Fig. 4. Right ear. Basal turn of the cochlea shows a total loss of Corti's organ, absence of the dendritic nerve fibers in the spiral lamina, atrophy of the tectorial membrane, and absence of the interdental cells in the spiral limbus. (H & E, X 253).

changes in the hair cells of the middle portion of the basal turn, with maximal damage occurring in the region 10-12 mm from the basal end of the cochlea. Recently, McGill and Schuknecht[5] reported six cases of noise-induced hearing loss with close correlation between the permanent auditory threshold shifts and the spatial locations of the sensory lesions. The maximum degenerative change in the hair cells was confined to the area 9-13 mm from the basal end. The loss of outer hair cells was more severe than that of inner hair cells. They also observed neuronal degeneration in five cases.

The pathological findings observed in our case are identical to those produced in animals by intensive noise[6] and appear to be due in this case mainly to the industrial noise explosions suffered by the patient. In addition, our case with a profound hearing loss shows more severe pathological findings in the organ of Corti and in the spiral ganglion cells and a much more extended lesion in the cochlea than did those cases previously reported.[2-5]

Regarding the extensive lesion caused by noise trauma in this case, Stockwell et al[7] reported that a lower frequency noise produced greater damage to the outer hair cells than a higher frequency noise, and that the damage extended from the supposed sites of maximal stimulation toward the basal end of the cochlea. The major loud noises to which this patient was exposed were frequent explosions of dynamite and noise from drilling machines in the enclosed space of the gold mine. Presumably these noises included more intensive and lower frequencies than those of previously published cases,[2-5] who had been exposed to factory, engine room, and gunfire noise.

An interesting and important observation in this case is that the patient's hearing loss progressed even in the ten-year period after he retired from his gold mining business (1959-1969) (Fig. 1). At the time he retired in 1959, he was 59 years old and had already had diabetes mellitus for several years. In view of this contributive medical history and the audiometric findings, aging and/or diabetes mellitus should be considered as additional causative factors for the profound deafness and cochlear pathology seen in this case.

Schuknecht[8] classified presbycusis into four categories: 1) sensory presbycusis, 2) neural presbycusis, 3) strial presbycusis, and 4) cochlear conductive presbycusis. The pathological findings observed in our case (hair cell atrophy, loss of cochlear neurons, and strial atrophy) might have been due to a concomitance of three of the types (1-3) of presbycusis mentioned above. In particular, the patchy strial atrophy which is one of the characteristic findings in aging is more likely to be a result of aging than of noise trauma, since no histopathological report on noise trauma has identified this atrophy as characteristic.

With respect to inner ear pathology in diabetes mellitus, Costa[9] found PAS-positive deposits in the vascular walls of the stria vascularis of diabetic albino rats. Similar changes in the human inner ear were observed not only in the stria vascularis[10] but also in the modiolus.[11] In addition, Makishima and Tanaka[11] reported atrophy of the spiral ganglion in diabetic individuals. In our case, no deposits in the inner ear vessels were observed, but there was a loss of cochlear nerve fibers in the ear where Corti's organ was severely atrophic. In the present case, it is difficult to indict diabetes mellitus as a major etiological factor, but it may also be difficult to exclude it as an associated etiological factor, particularly in regard to the neural pathology.

In our case, the spiral ganglion cells were markedly decreased in number in the middle and basal turns where Corti's organ was markedly destroyed. This finding could represent retrograde neuronal degeneration secondary to destruction of the supporting cells in Corti's organ,[12] loss of the inner hair cells,[4] and/or direct damage to the peripheral dendrites to the inner hair cells[13] as a result of industrial noise exposure. The presence of a few remaining ganglion cells in these turns appears to be similar to the findings of Spoendlin.[13] An additional finding of interest was observed in the same region. The dendritic nerve fibers were almost absent in the osseous spiral lamina, whereas some of the axonal nerve fibers were present in the modiolus. An interesting question still open for discussion is whether or not the retrograde neuronal degeneration was in process as late as ten years after the patient's retirement from the mining business.

The physiological significance of the loss of the interdental cells is not clearly understood, although Lim[14] and Voldrich[15] reported that they seem to be associated with some secretory activity. In our case, the atrophy of the limbus with absence of interdental cells occurred sporadically in the middle and basal turns. The abnormalities of the tectorial membrane and of Reissner's membrane, however, do not appear to correlate in location with those in the limbus. Thus, the pathoetiology associated with the limbus atrophy remains unclear.

There are two clinically interesting points in our case. One is that the patient could hear only 250 Hz at 90 dB in the right ear. At present, differentiation of hearing from a vibratory sensation in the lower frequencies is not easy, especially in cases with profound hearing losses.* However, the following clinical data in this case appear to be in favor of hearing sensation: 1) for more than ten years the right ear had had better hearing in the low frequencies than the left ear, although the hearing loss was progressive bilaterally; and 2) the patient had no subjective sensation in the left ear for 250 Hz at 90 dB, yet he had a hearing sensation in the right ear at the same level of stimulation. Furthermore, the severity of the hair cell pathology in the upper middle turn and in the apical turn (26-32.5 mm) was found to be less in the right ear than in the left ear, particularly in the area 26-27 mm from the basal end. Schuknecht[12] reported that loss of the outer hair cells with a preservation of the inner hair cells results in a threshold elevation of about 50 dB, and that total loss of the outer hair cells with some inner hair cell loss is associated with a hearing loss greater than 50 dB. According to Koenig's scale,[16] (modified**) in humans with 32.5 mm total length of the cochlea the location of the frequency 250 Hz is 29.2 mm from the basal end. These data previously reported suggest that the remaining hair cells, particularly the inner hair cells, in the upper middle and apical turns (26-32.5 mm) especially in the area 26-27 mm from the basal turn in the right cochlea, might have played a role in the hearing response of 250 Hz at 90 dB.

Another interesting point is that the left ear was totally deaf, even though some of the hair cells and most of the cochlear nerve were present in the apical portion of the cochlea. In addition, there were some spiral ganglion cells and their axonal fibers remaining in the other parts of the cochlea all the way to the basal end, although the dendritic fibers and hair cells were mostly absent, particularly in the basal turn. They may raise questions about the indications and methods for cochlear implantation,[17] e.g., 1) whether or not effective stimulation and pitch discrimination for low frequencies can be obtained with the cochlear nerve and sensory cells preserved in the apical turn of the cochlea, as in our case where hearing was absent; 2) whether or not effective stimulation can be obtained when some ganglion cells and axons remain without their dendritic nerve fibers and hair cells in the basal turn where the electrodes may be placed. Further study in both the clinical field and in human temporal bone histopathology may be important to increase our knowledge on these interesting points.

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XII WORLD CONGRESS OF OTORHINOLARYNGOLOGY

The XII World Congress of Otorhinolaryngology will be held June 21-26, 1981 in Budapest, Hungary. Preliminary communications, recommendations and suggestions, should be directed to Prof. Dr. L. Surján, President, XII World Congress of ORL, H-1389 Budapest, Pf: 112 Hungary.

Ann Otol 87:1978

SURGICAL ANATOMY OF THE TEMPORAL BONE IN THE CHINCHILLA

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The chinchilla is of value in otological research for many reasons, including the surgical accessibility of the majority of structures within its temporal bone. This paper describes the anatomy of the chinchilla's temporal bone, and four surgical approaches to the labyrinth and ossicular chain, three through the bulla and the other via the external canal. No one approach reveals all the temporal bone structures, and each route is therefore more suited to some surgical procedures than others. The cochlea is particularly accessible for microsurgical procedures because it projects into the labyrinthine part of the bulla and because its bony capsule is thin. Surgery in the posterior cranial fossae is both hazardous and difficult; the hazard is bleeding from the venous sinuses which run within the occipital and temporal bones, and the difficulty is the limited access due to the intervening cerebellum and the closeness of the brain stem.

The chinchilla (*C. laniger*) is a rodent, distantly related to the guinea pig, whose use in otological research was initiated by Rasmussen and thereafter pioneered by Miller.[1] This use is increasing because, apart from its comparative cheapness to buy, house and maintain, the chinchilla's large bullae allow firm head fixation and easy surgical access for electrophysiological recording and it can be trained in behavioral audiometry.[2-4]

Though the chinchilla has been used for over 15 years in basic otological research, there is no description in the literature of the anatomy of its temporal bone, which is an obvious requirement if its use is to increase. This paper, therefore, describes the surgical anatomy of the chinchilla's temporal bone using *Anatomy of the Guinea Pig*[5] for ascribing comparative anatomical terms.

TEMPORAL BONE ANATOMY

The temporal bone is the largest single bone in the chinchilla skull (Figs. 1 and 2) due to the size of its bulla, the paired bones along with the occipital bone encasing the cerebellum and brain stem. Surgery in any of the skull bones can be hazardous as the venous sinuses run within the bone rather than in the dura (Fig. 2). Paired transverse sinuses encircle the dorsal part of the bulla and drain either to the zygomatic venous system or to the superior sagittal sinus in the midline. In the occipital bone above the foramen magnum the sagittal sinus divides into the lateral sigmoid sinuses which run a variable course in the marrow before continuing in the synarthrosis between the occipital and temporal bones to connect with the jugular venous system. For anatomical purposes the temporal bone can be described under four headings: 1) bulla; 2) external auditory canal and tympanic ring and membrane; 3) ossicular chain; and 4) labyrinth.

BULLA

Despite the size of the bulla its bone is paper thin, its strength being derived from the large, but variable, number of internal septa (Fig. 3). The dorsal part of the bulla is subcutaneous and, therefore, palpable except for the anterior and posterior rims where the

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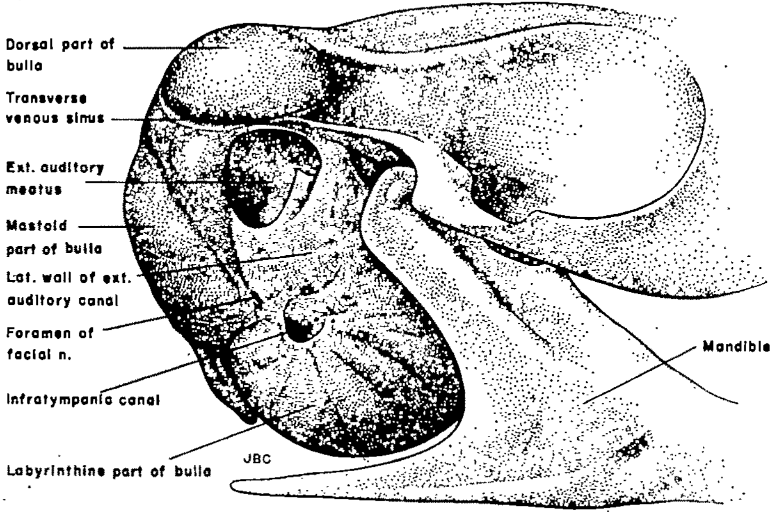

Fig. 1. Lateral view of the chinchilla's right temporal bone, its relatively large size in comparison with the remainder of the skull being due to its large bulla. The external auditory canal is a tunnel running superficially within the temporal bone whose lateral wall is continuous with and in the same plane as that of the mastoid and labyrinthine part of the bulla.

temporal and platysma muscles respectively are attached. The mastoid part of the bulla, which is divided internally by a septum, cannot be felt because the occipital muscles arise from its entire surface. By contrast, the labyrinthine part of the bulla is readily palpable in the neck even though the digastric muscle originates from its surface. Within the bulla there are several bone struts which support the tympanic ring. The apex of the cochlea is also supported by two struts, the more dorsal of these being a useful landmark for finding the Eustachian tube (Fig. 3). The entire bullar system is thus aerated via the Eustachian tube in the labyrinthine part of the bulla through a large middle ear space. The bulla is lined with a single layer of mucosa except in the area of the Eustachian tube, where the lining is pseudostratified, ciliated, columnar epithelium.

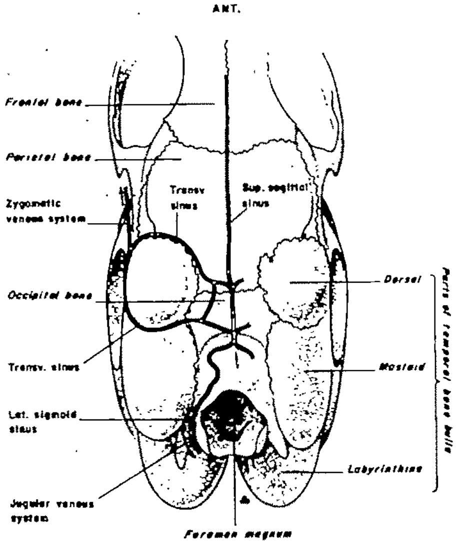

Fig. 2. Posterior-superior view of the skull illustrating, on the left side, the venous sinuses which run within the parietal, temporal and occipital bones. The course, particularly within the last, is variable.

EXTERNAL AUDITORY CANAL AND TYMPANIC RING AND MEMBRANE

In the chinchilla the tympanic membrane is difficult to see even with a speculum, partly because of the cartilaginous folds of the auricle but mainly because the canal runs dorsal-ventral within the temporal bone, the lateral wall being continuous with, and in the same plane as, the lateral walls of the labyrinthine and mastoid parts of the bulla. The tympanic ring and mem-

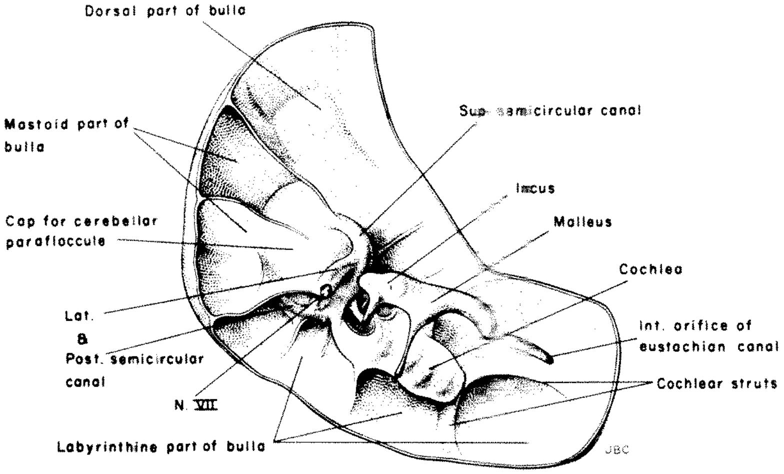
Dorsal part of bulla
Sup. semicircular canal
Mastoid part of bulla
Incus
Malleus
Cap for cerebellar paraflocculi
Cochlea
Lat. & Post. semicircular canal
Int. orifice of eustachian canal
Cochlear struts
N. VII
Labyrinthine part of bulla
JBC

Fig. 3. Lateral view of the right temporal bone displaying the structures of the middle ear, the bone of the lateral walls of the bulla having been removed and the tympanic membrane detached from the malleus handle. Note the multiple bone struts which buttress the thin temporal bone as well as demarcating the boundaries of the bulla compartments. The malleus and incus are fused. A useful landmark for the internal orifice of the Eustachian canal is the most dorsal of the cochlear bone struts.

brane are set in the medial wall of the canal and are therefore in the same plane as the line of vision. The thin tympanic membrane sits within the bony tympanic ring and is very mobile, as can be seen by direct observation during respiration and as shown by tympanometry.[6]

OSSICULAR CHAIN

The incus and malleus (Fig. 3) are fused by cartilage, their bodies being in effect a horizontal bar. The manubrium of the malleus is extremely thin but derives extra strength from its T-shaped cross section. The long process of the incus articulates with the stapes at the incudostapedial joint, the stapedius tendon being attached to the posterior crus of the stapes (Fig. 4). Compared with man, the crura are more centrally placed on the footplate and a bone strut passes through the arch from the fallopian canal to the rim of the round window. It has been suggested[5] that this represents the remnant of the stapedial artery which can be found in a comparable position in the bat and sev-

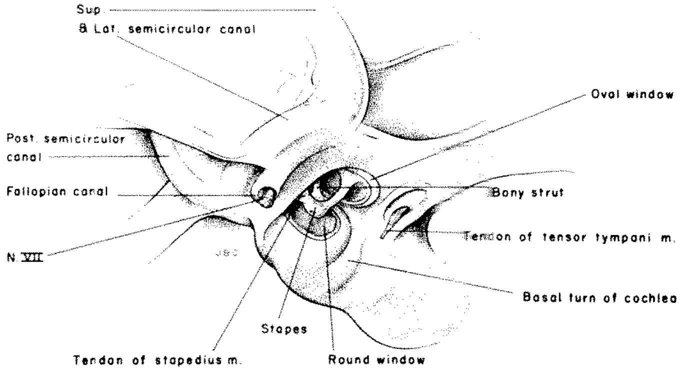

Fig. 4. The labyrinth and cochlea in greater detail than in Fig. 3, the incus-malleus having been removed.

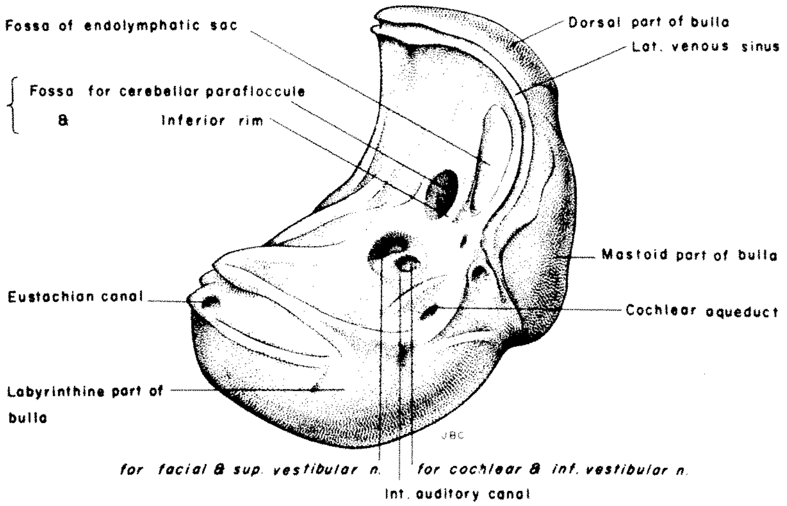
Fossa of endolymphatic sac
Dorsal part of bulla
Lat. venous sinus
Fossa for cerebellar paraflocculus
&
Inferior rim
Mastoid part of bulla
Eustachian canal
Cochlear aqueduct
Labyrinthine part of bulla
JBC
for facial & sup. vestibular n.
for cochlear & inf. vestibular n.
Int. auditory canal

Fig. 5. Medial view of the right temporal bone, as seen from the posterior cranial fossa.

eral other animals, but ossification of such a structure would appear unlikely and the histology does not show any arterial remnant. The tensor tympani arises in the bony tunnel anterior to the oval window and attaches to the incus-malleus.

LABYRINTH

The cochlea of 3½ turns projects into the labyrinthine part of the bulla (Fig. 3). The normal histology has been well documented,[7] the organ of Corti being on average 18.4 mm in length with 102 inner and 405 outer hair cells per millimeter. The hair cells are innervated by the cochlear division of the VIII nerve, which takes a short course directly through the shallow internal auditory canal (Fig. 5) to the modiolus. The cochlear nerve contains on average 23,500 nerve fibers.[8] The vascular pattern of the chinchilla cochlea has also been well described.[9]

The semicircular canals (Figs. 3 and 4) can be readily identified encircling the bone cap which projects into the bulla and encases the parafloccular lobe of the cerebellum. The lateral canal runs alongside the fallopian canal before encircling the inferior part of the bone cap. The posterior canal encircles the inferior part of the bone cap only and the superior canal, after running over the cap in the dorsal part of the bulla (Fig. 3), then encircles the rim of the cap in the medial aspect of the temporal bone. The membranous labyrinth is innervated in the conventional manner by the vestibular nerve which has two distinct branches, the superior and inferior, these entering the internal auditory canal with the cochlear and facial nerves respectively (Fig. 5). Figure 5 illustrates the medial aspect of the temporal bone as seen from the posterior cranial fossa. The fossa for the parafloccular lobe of the cerebellum is an important landmark because both the superior semicircular canal and the vestibular aqueduct run in the inferior rim. The endolymphatic sac occupies a bony depression (foveate fossa) between this rim and the lateral sigmoid sinus. The cochlear aqueduct opens inferiorly to the internal auditory meatus.

The facial nerve enters its fallopian canal in the internal auditory canal, runs above the oval and round windows, crosses the middle ear posterior to the external auditory canal to exit via its foramen (Figs. 1 and 4). This should not be confused with the infratympanic recess which contains only fibrous tissue.

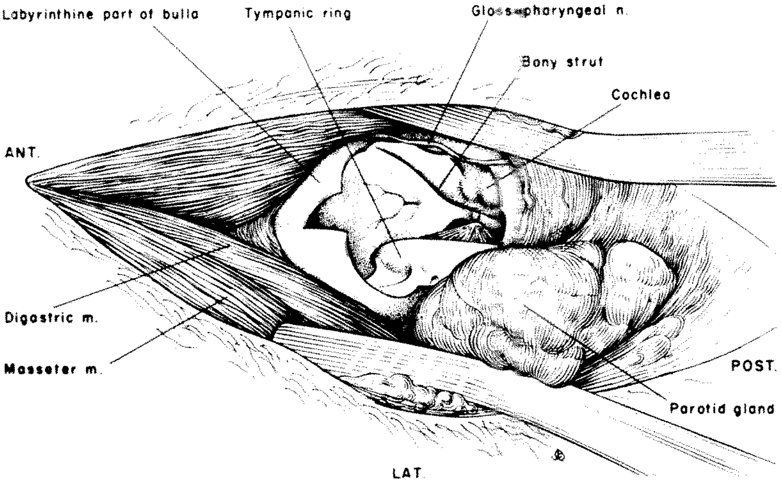

Fig. 6. Surgical view of the labyrinthine part of the right bulla, in this instance the digastric muscle has been detached and retracted laterally. The ready access to the apex of the cochlea and to the Eustachian canal via the bone strut can be appreciated.

SURGERY

ANESTHESIA

The use of sodium pentobarbital has been reported,[2] but we prefer the combination of ketamine hydrochloride (Ketalar®) 65 mg/kg of body weight injected into the thigh muscles with atropine 60 μg intraperitoneally because of its speed and reliability. Anesthesia occurs within 30 minutes and lasts up to 60 minutes. If a longer period is required, supplements of 7.5 mg of intramuscular ketamine hydrochloride may be given. For anesthesia of up to ten minutes, say for venesection, 7.5 mg of intramuscular ketamine hydrochloride alone is satisfactory.

APPROACHES TO THE MIDDLE EAR

As no single approach gives access to all the middle ear structures, four distinct surgical routes have been utilized, three being through the bulla and the other being through the external auditory canal.

Bulla Approaches.

1. Through the dorsal part of the bulla the fused part of the incus-malleus, the superior aspect of the tympanic membrane, and the superior semicircular canal are accessible. To date[4] this approach has been used to remove the incus-malleus to create a conductive hearing loss to protect the cochlea from noise induced trauma, this cochlea subsequently being used as a histological control for the contralateral noise damaged side. Since the fallopian canal overhangs the oval and round windows, access to these and other inferior structures is not possible. The dorsal part of the bulla is readily identified by palpation and by its outline on the back of the head. After incising the skin and subcutaneous tissues, the bulla at this site is easily cut with a pointed scalpel blade and the desired amount of bone removed or a bone cap raised as a free or as a hinged flap.

2. Through the labyrinthine part of the bulla (Figs. 3, 6) the cochlea, the Eustachian tube orifice and the inferior tympanic ring and membrane can be reached directly and the round window indirectly. This approach is commonly used to ablate the cochlea (see below) but would be ideal for creating localized lesions, such as to Reissner's membrane, basilar membrane, hair cells and stria vascularis, provided the technical difficulties of creating small lesions could be overcome. Sampling of endolymph and perilymph would also be possible as would attachment of round window electrodes. Serous otitis media

can be reliably created by stripping the mucosa in the area of the Eustachian tube orifice, then plugging this with bone wax.

The labyrinthine part of the bulla is identified by neck palpation and a longitudinal incision is made through the skin, subcutaneous tissues and platysma. The parotid gland, which lies medial to the mandible and the masseter muscle, is retracted after incising its fascia. The digastric muscle can be detached, split or retracted medially or laterally from its attachment to the bulla. Medial retraction can injure the glossopharyngeal nerve or provoke bleeding from tributaries to the jugular vein. Anoxia is an additional danger secondary to direct tracheal compression or laryngeal nerve palsy, especially following bilateral operations. Approaching lateral to the digastric muscle is more confined than the other approaches, but there is no danger of damage to important structures and it does allow more direct vision of the Eustachian tube orifice. The bulla wall is readily trephined and the desired area of bone can then be removed with forceps. Following surgery this opening closes spontaneously, initially with fibrous tissue, and then with bone in about four weeks.

3. A combined approach through the mastoid and labyrinthine parts of the bulla can expose the fallopian canal, the round window and the posterior and lateral semicircular canals. By extending through the septa into the dorsal part of the bulla the superior semicircular canal becomes accessible and thus would be the approach of choice to fenestrate, fistulize or obstruct the semicircular canals. The infratympanic portion of the facial nerve would be best stimulated, sectioned or recorded from, via this approach. Cochlear ablation and recording from the round window can also be performed this way as well as through the labyrinthine part of the bulla.

For this approach the animal's neck must be flexed to allow adequate inferior access. A longitudinal skin and subcutaneous incision is made in the neck between the external ear and the midline exposing the dorsal part of the bulla and the cervicoauricular muscle. This muscle along with the underlying platysma is detached from the temporal bone bringing into view the mastoid part of the bulla, separated from the dorsal part of the bulla by a transverse venous sinus. Once the splenius muscle is detached, the entire mastoid part of the bulla and the posterior portion of the labyrinthine part of the bulla are accessible. The mastoid part is trephined and the opening enlarged. The septum between the mastoid and the labyrinthine parts is removed and access to the round window is then possible below the fallopian canal.

Approach Via the External Auditory Canal. This is the most direct approach to the tympanic membrane, ossicular chain and oval and round windows. This would therefore be the approach of choice for experimental myringoplasty, tympanoplasty, ossicular fixation and stapedectomy. Partial auriculectomy may be performed at the same time to facilitate access and allow subsequent direct observation of the tympanic membrane. A semicircular incision is made below the ear, keeping close to the auricular cartilage to avoid injury to the facial nerve inferiorly. The subcutaneous connective tissue is stripped down to the periosteum of the lateral canal wall. Division of the periosteum at the canal rim allows the thin skin and periosteum to be elevated, and the bone of the lateral canal wall can then be totally removed. A vertical incision of the canal skin and periosteum exposes the tympanic membrane and a tympanomeatal flap can be elevated to gain access to the middle ear. As it has been found impossible and indeed unnecessary to appose the edges of the canal skin, only the initial incision requires suturing.

Partial auriculectomy is preferable to a total auriculectomy as the rim of cartilage that is left can be varied, but a rim of about 1 cm also obviates the problem of the canal becoming obscured with fur. When the partial auriculectomy is performed along with an external canal approach, the skin incision is completed around the base of the ear. After dividing the blood vessels, the auricular muscles and soft tissue are stripped off the perichondrium and the ear amputated at the desired level. Any excess tissue can then be trimmed and the external skin sutured through the cartilage to the canal skin.

APPROACH TO THE POSTERIOR CRANIAL FOSSA

Theoretically the thinness of the chinchilla temporal bone should make posterior fossa surgery rewarding, but the problems of bleeding from the venous sinuses, the closeness of the brain stem and the difficulty of access to the intracranial structures make it extremely difficult and hazardous. Through the posterior cranial fossa it is possible to approach the endolymphatic sac and the endolymphatic duct in the vestibular aqueduct below the parafloccular lobe of the cerebellum.[10] Because of the difficulty of visualization, transection of the facial, cochlear or vestibular nerves in the internal auditory canal has not been accomplished without brain damage incompatible with long-term survival. For electrophysiological recording, where survival of the animal after recording is not necessary, the cerebellum can be aspirated to expose the cochlear nucleus but auditory nerve recording has to be blind through the cochlear nucleus as further aspiration has depressed the gross action potential. Brain stem recordings and lesions should be possible with this approach.

Through a transverse neck incision the occipital muscles are divided at their attachment to the mastoid part of the bulla and the occipital bone. Bleeding inevitably occurs from the venous sinuses within the occipital bone when this is removed for access, but can usually be controlled with bone wax. It is preferable to retain the rim of the foramen magnum to protect the brain stem but otherwise sufficient bone must be removed to allow adequate access without excessive brain retraction, as the chinchilla tolerates this poorly, most likely because of brain stem damage.

COCHLEAR ABLATION

In auditory research it is often necessary to destroy the hearing on one side by ablation of the cochlea so that results can be attributed to one ear. However, the efficacy of the ablation has to be confirmed by histology.

Cochlear ablation can be performed through the labyrinthine part of the bulla, the apex and apical two turns being amputated and the auditory nerve macerated in the modiolus. Postoperative symptoms are usually minimal with no vestibular upset. It is possible to uncap all the turns to the round window but this increases the risk of permanent vestibular dysfunction and the consequent motor disability may interfere with behavioral audiometry. The round window can also be approached below the fallopian canal through the mastoid and labyrinthine parts of the bulla and the cochlea's lateral wall outfractured.[2] An alternative to cochlear ablation is to remove the incus-malleus body to create a conductive loss of 40-50 dB which is often sufficient. This also retains a control cochlea for histology.[4]

CONCLUSIONS

The anatomy of the chinchilla's temporal bone is considerably different from man's, some of the differences being beneficial and others detrimental to surgical access. For example, ready access to some structures is possible because of the large size of the bulla: the incus-malleus complex via the dorsal part of the bulla, the cochlea and internal orifice of the Eustachian tube via the labyrinthine part of the bulla and the semicircular canals via a combination of the mastoid and labyrinthine parts of the bulla. The oval window and stapes can only be approached via the external auditory canal through the tympanic membrane and this is slightly more exacting due to the dorsal-ventral angle of the canal.

Posterior fossa surgery is extremely

difficult because of two factors. The first is that the venous sinuses run within the occipital and temporal bones making bleeding unavoidable and difficult to control when removing bone for access. The second is that the structures most often approached through the posterior fossa, the cochlear and vestibular nerves and the endolymphatic duct and sac, are extremely difficult to reach because of intervening cerebellum, especially the parafloccular lobe, and the proximity of the brain stem.

There are other minor differences in the anatomy compared with man which, though present in many other animals and of little practical consequence, should be appreciated by those working with chinchillas. Thus the incus and malleus are fused, there is a bone strut between the stapes crura, and the tensor tympani is attached to the manubrium of the malleus.

Because the chinchilla's hearing is relatively susceptible to noise trauma, because it can be trained in behavioral audiometry and because the relative thinness of the cochlear bone makes histologic preparation comparatively easy, the chinchilla will be increasingly used in otological research. The direction which this takes will, however, be greatly influenced by the anatomy of its temporal bone.

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SPECIAL HEAD AND NECK CANCER FELLOWSHIP

The Special Head and Neck Cancer Fellowship of the American Society for Head and Neck Surgery at the M.D. Anderson Hospital beginning July 1, 1979 has been awarded to Dr. Robert H. Nelson of the Department of Otorhinolaryngology, University of California, Sacramento. With the fellowship goes an honorarium of $5,000.

BOOK REVIEWS

Advances in ORL, Volume 24: Modern Methods of Radiology in ORL

Edited by *S. Brünner* and *P. E. Andersen*. Hard cover, illustrated, 196 pp, 1978. S. Karger, White Plains, NY. Price $72.50

This volume is a compilation of selected papers from the Seventh International Congress of Radiology and Otorhinolaryngology held in Copenhagen, Denmark, May 31-June 2, 1976. Heavy emphasis is placed on computerized axial tomography (CAT) with 7 of the 19 papers directed to this area. It is very properly pointed out that CAT is most useful in the diagnosis of acoustic neurinomas and meningiomas when infusion of contrast is carried out and that intracanalicular lesions as well as small tumors of the cerebellopontine angle are difficult to define with CAT examination only. Both advantages and shortcomings of CAT are well-covered by Schindler et al and Carter et al. The observation is made that in many instances, the CAT scan has obviated the necessity of invasive studies. An interesting discussion of cerebral spinal fluid fistula or "gusher" is related by Phelps and Lloyd. Two articles, one by Lilie Quist and another by Valvassori, emphasize the long neglected syndrome of VII nerve neurinomas. Wilbrand et al present fantastic examples of their ability to make a plastic mold of the human inner ear along with pertinent observations concerning the vestibular aqueduct as seen in tomography in Ménière's disease. The abnormally small and abnormally large vestibular aqueduct is considered by Valvassori and Clemis. Unger et al explore the value of hypocyloidal polytomography in evaluation of chronic nasal and paranasal sinus disease and conclude that this technique is more accurate in delineating pathology in these conditions than conventional roentgenography. Zizmore and Noyek present interesting films on the calcifying and osteoblastic tumors of the nasal and paranasal cavities. Chiesa and Acciarri emphasize the additional information to be gained and the limitations of thermography of the neck. They stress that thermography alone is not sufficient for an exact definition of the nature of the lesion.

The collection of papers concludes with a discussion of the usefulness of bone scintigraphy and tomography in diseases of the paranasal sinus and base of the skull by Frey et al. They demonstrate that tomography and scintigraphy are complimentary in the diagnosis of many head lesions. Reproductions of the roentgenograms are largely of good quality throughout the volume. In a number of instances, further advances in head and neck roentgenography in the past two years have made the papers a trifle outdated. The book is never the less a good one for basic information on the selected subjects mentioned above for either the radiologist or otolaryngologist.

J. WILLIAM WRIGHT, JR., MD
Indianapolis, IN

Diagnostic E.N.T.

By *G. D. L. Smyth*. Paperback, black and white illustrations, indeved, 124 pp, 1978. Oxford University Press, New York. Price $8.95

This new textbook is directed at medical students, to whom the problem-oriented approach should be particularly appealing. The author considers 17 common otolaryngologic symptoms and signs, discusses the pertinent anatomy and physiology and makes practical recommendations for treatment. He also defines the indications for further evaluation and referral. He concludes most chapters with an outline of the major causes of each symptom that has been discussed.

The selection of topics is appropriate and the book is well organized. The presentation is generally clear, concise and factual. The numerous line drawings are particularly helpful in supplementing the text. Although the more inquisitive or experienced reader might desire some assistance in locating further information about the topics covered, the author unfortunately does not include a list of selected references. Nevertheless, this book should be of interest to many medical students who desire a self-contained, elementary and reliable introductory text.

FRANK E. LUCENTE, MD
Elmhurst, NY

Progress in Clinical Neurophysiology, Vol I: Attention, Voluntary Contraction and Event-Related Cerebral Potentials

Edited by *John E. Desmedt*. Hard cover, black and white illustrations, indexed, 256 pp, 1976. S. Karger, Basel, Switzerland. Price $37.75

This volume is part of a comprehensive project designed to encompass all aspects of event-related potentials. It consists of contributions from investigators with considerable experience in this area. Its purpose is to communicate recent information on brain potentials related to attention and motor control in normal and pathological states.

The book is divided into three sections. The first section, "Methodology and Publication Criteria," includes guidelines for publication of event-related potential data, and a comprehensive discussion of variables and sources of artifact affecting various parameters of the recorded potentials. The necessity of communicating information such as instrumentation calibration data for a better understanding of the results by the reader, is stressed. The second section, "Reconsideration of the Cerebral Mechanisms Underlying Selective Attention and Slow Potential Shifts" explores the neurophysiological mechanisms that regulate event-related potentials and attention. The interaction between the thalamic reticular nucleus, mesencephalic reticular formation and the mediothalamic-fronto-cortical system is supported by experimental data and is discussed in detail. The effects of various behavioral conditions preceding motor responses on the topographical distribution of slow potential shifts recorded at the scalp in humans are also discussed. The last section, "Event-Related Cerebral Potentials and the Initiation of Voluntary Contraction" deals with potentials preceding voluntary movement and explores their significance. The Bereitschaft potential, premotion positivity and the various components of the motor potential recorded at the scalp and from thalamus in humans and primates are discussed and examined. Inferences are made on the neurophysiological mechanisms underlying voluntary movement based on recordings made from normal subjects and patients with bilateral or unilateral Parkinson akinesia. This volume contains useful information for investigators involved in movement physiology, those interested in cognitive processes, and to clinicians to the extent that it includes clinical data that may help differentiate between various CNS diseases affecting movement.

Paul Kileny, PhD
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Progress in Clinical Neurophysiology, Vol 2: Auditory Evoked Potentials in Man and Psychopharmacology Correlates of Evoked Potentials

Edited by *John E. Desmedt*. Hard cover, black and white illustrations, indexed, 212 pp, 1977. S. Karger, Basel, Switzerland. Price $37.75

This volume discusses the clinical relevance of current methods for assessing the auditory evoked potentials in normal and research subjects and in clinical patients and describes how these evoked potentials can be used to evaluate objectively new neuroleptic and psychoactive drugs. The book consists of numerous short articles representing current thought in this area. The editor is to be commended for his choice of authors, for avoiding overlap, and for his attempts to implement some standard nomenclature in a very confused area because of the inconsistencies of terminology.

Many of the chapters reflect the current, intense interest in the early time-locked potentials, the "brainstem auditory evoked potentials." Most of the brainstem potential data were derived from normal subjects and a few early studies of patients with peripheral and central disease states. No large studies with long-term follow-up are as yet available.

In contrast, the chapter, "Assessment of Auditory Sensitivity in Infants and in Uncooperative Handicapped Children by Using the Late Components of the Average Auditory Evoked Potential" recounts the experience of testing over 400 children, and is a model of clarity of expression and thought which should be required reading for anyone involved in evoked potential testing.

Another interesting chapter documents auditory abnormalities in multiple sclerosis patients who often have no auditory or other brainstem symptoms. This complements previous information from the visual pathways pointing out the high incidence of asymptomatic placques which can be detected by evoked potential recordings.

The chapters are well-written and the type is easily read. As a representation of the "state of the art" in a very rapidly changing field, the book will be out of date in some areas quite soon. However, it is a useful text, well-compiled, and a valuable source book.

Lee A. Harker, MD
Iowa City, IA

Progress in Clinical Neurophysiology, Vol 3: Language and Hemispheric Specialization in Man: Cerebral Event-Related Potentials

Edited by *John E. Desmedt*. Hard cover, black and white illustrations, referenced, indexed, 288 pp, 1977. S. Karger, Basel, Switzerland. Price $47.25

This book is comprised of 18 papers and is divided into four main chapters. Each chapter contains two to nine papers. The first chapter is an introduction which covers background and presents general concepts of the cortical and subcortical mechanisms involved in speech and language. The second and third chapters deal with speech perception and speech production. In the last chapter, different research procedures and new data bearing on lateralization in the human cerebral cortex and hemispheric asymmetry in event-related potentials [ERP] as signs of sensory processes are presented.

In general, the book is very well organized and illustrated. Its goal is to advance the understanding of hemispheric specialization in the human cerebral cortex in relation to language and nonlanguage cognitive processes using the methods of direct electrophysiological recording of brain electrogenesis. The book's strength lies in three areas. First, it contains a comprehensive overview of the topic. Thus a basic or clinical neurophysiologist wanting a brief introduction would profit by reading it. Second, it presents critical new data and views bearing specifically on those problems of ERP correlates of hemispheric specialization in man. And third, it introduces various procedures for studying hemispheric specialization in man and points up some of the inadequacies of earlier work. This book will serve as a valuable reference to neurophysiologists and neurosurgeons.

J. H. Ryu, MSE
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ABSTRACTS FROM NATIONAL AND INTERNATIONAL JOURNALS

Management of Malignant Tumor of the Tonsil

Inouye K, Kikawada K: Pract Otol (Kyoto) 71:235-242, 1978

A clinical survey was done on 99 patients with malignant tumor of the palatine tonsil. Histologically, 81 cases revealed sarcoma, including 73 reticulum cell sarcoma cases. The patients were treated by radiotherapy and surgery at Tokyo University Hospital through interdisciplinary collaboration during the period of 1964-1976. Radiotherapy was applied first to the primary lesion (81 cases) and metastases (48 cases) of all sarcoma patients, except one whose gastric metastasis was treated by surgery alone. Surgery or systemic administration of chemotherapeutic agents were supplemented to six cases with primary tumors and seven cases with metastasis. For all 18 carcinoma patients, irradiation was primarily given to the tonsil and metastasis (8 cases). Regional chemotherapy was also given to three patients with primary tumors, and systemic administration of chemotherapeutic agents was added to one case with metastasis. No surgery was required in cases of carcinoma. The five-year survival rate was 57% in sarcoma cases and 70% in carcinoma cases. The following is concluded: For tonsil sarcoma, irradiation to the primary lesion and metastasis is so very effective that neither surgery nor chemotherapy is necessary. In cases of carcinoma, radiotherapy should be applied first to the primary tumor and the metastasis. Regional chemotherapy can be combined for some radioresistant cases.

M. Igarashi

Rhinocerebral Mucormycosis

Cruickshank G, Vincent RD, Cherrick HM, et al: J Am Dent Assoc 95:1164-1168, 1977

A case of rhinocerebral mucormycosis which resulted in death 11 days after hospital admission was presented. The patient was a 48-year-old Caucasian woman who had been a brittle diabetic for 20 years taking 38 units of protamine insulin a day. She presented to her dentist four days before admission and was treated with local measures for ulceration and severe pain in the left maxillary vestibule with moderate swelling and discoloration in the left cheek without improvement. On admission she was treated with amphotericin B therapy. First biopsy proved negative for mucormycosis. On second biopsy, the fifth day, mucormycosis was proved. Despite intensive measures patient expired on the 11th day. Autopsy findings showed maxillary left sinusitis with extension into adjacent sinuses, mouth, skin, brain; diabetic ketoacidosis; occlusion of right coronary artery with emboli associated with myocardial infarction of left ventricle and papillary muscle; areas of infarction of left lung. Extension into the brain was noted with culture positive for mucormycosis. The article points up the necessity of awareness of this fulminating entity and its early diagnosis for the dentist since it has been shown that vigorous medical and surgical treatment have reduced mortality from 90% to 50%.

J. D. Piro

A Review of Controversial Diagnostic and Therapeutic Techniques Employed in Allergy

Golbert TM: J Allergy Clin Immunol 56: 170-190, 1975

Golbert has comprehensively reviewed the subject in this paper, which is recommended reading for all physicians who care for patients with allergic or allergic-like diseases. Included in his scrutiny are titration, provocative testing, sublingual desensitization, and leukocytotoxic tests. The author concludes with the following opinions:

1. The leukopenic index and the pulse test have not been compatible with basic scientific or clinical scientific data during the past 20 years.

2. Intracutaneous titration as a guide to "optimal dose," intracutaneous and sublingual provocative testing, and the leukocytotoxic test have not been supported by basic or controlled clinical research. Neither diagnostic nor therapeutic validity has been substantiated for any of these procedures.

3. Measures to eliminate the roles of suggestion and bias in either patient or physician relative to these diagnostic and therapeutic techniques have not been described.

4. Therefore, continued use of these procedures in the care of patients has not been justified.

In an accompanying editorial, Francis C. Lowell points out that controversial procedures in allergy must undergo appropriate evaluation, and that this evaluation is characteristically and appropriately carried out by the technique's proponents. Accepted standards of scientific validation are required, and have not been applied by those proponents who enthusiastically teach and use these techniques clinically.

Controversial techniques may be used to evaluate patients with straightforward atopic allergy. More often they are applied to patients with bothersome symptoms for which no allergic basis can be found using conventional techniques. We, as physicians, are frustrated by such symptomatic patients who demand a diagnosis and cure. Science is often wanting and this justifies the use of art in medicine until science catches up. We must not succumb to pseudoscience, however, in the meantime.

H. B. Richardson

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CURRENT CLINICAL CONCEPTS IN OTOLARYNGOLOGY, 1979

Sponsored by
DEPARTMENT OF OTOLARYNGOLOGY
UNIVERSITY OF MIAMI
SCHOOL OF MEDICINE
at
Doral Country Club and Hotel
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January 15-18, 1979

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OTOLARYNGOLOGY 1979

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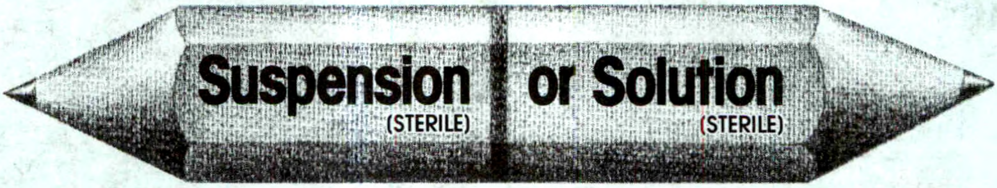
Every precaution is taken to insure accuracy, but we cannot guarantee against the possibility of an occasional change or omission in the preparation of this index.

Please don't just ℞ "Cortisporin® Otic"... Specify:

(polymyxin B-neomycin-hydrocortisone)



INDICATIONS:
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DESCRIPTION:
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The vehicle contains the inactive ingredients cetyl alcohol, propylene glycol, polysorbate 80, purified water and thimerosal (preservative) 0.01%.

PRECAUTIONS:
This drug should be used with care in cases of perforated eardrum and in long-standing cases of chronic otitis media because of the possibility of ototoxicity caused by neomycin.

ADVERSE REACTIONS:
Neomycin is a not uncommon cutaneous sensitizer. There are articles in the current literature that indicate an increase in the prevalence of persons sensitive to neomycin.

BENEFITS:
Indications include infections of mastoidectomy and fenestration cavities caused by organisms susceptible to the antibiotics.

INDICATIONS:
For the treatment of superficial bacterial infections of the external auditory canal caused by organisms susceptible to the action of the antibiotics.

DESCRIPTION:
Each cc contains: Aerosporin® brand
Polymyxin B Sulfate .... 10,000 units
Neomycin Sulfate .... 5 mg
(equivalent to 3.5 mg neomycin base)
Hydrocortisone .... 10 mg (1%)
The vehicle contains the inactive ingredients glycerin, hydrochloric acid, propylene glycol, purified water and potassium metabisulfite (preservative) 0.1%.

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ADVERSE REACTIONS:
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AUDITORY PROSTHESES RESEARCH with MULTIPLE CHANNEL INTRACOCHLEAR STIMULATION in MAN

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The authors thank the volunteers and their families for the many hours they have spent making these experiments possible.

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PREFACE

This month marks the tenth anniversary of the University of Utah's Neuroprostheses Program. Our research on aids for the blind based on visual cortex stimulation progressed in 1971 to include analogous aids for the deaf based on auditory cortex stimulation.

In 1973 this in turn led to a third, parallel effort — intracochlear stimulation. Spurred by the unflagging support of our volunteers and their families, this project has since expanded to involve three principal institutions — the University of Utah in Salt Lake City, the Ear Research Institute in Los Angeles, and the College of Physicians and Surgeons of Columbia University in New York City.

Dr. Derald Brackmann has been responsible for all of the surgical procedures, assisted by Dr. James Parkin. Dr. Michael Mladejovsky has played a key role in development of computer hardware and software. However, Dr. Donald Eddington has had responsibility for all of the day-to-day physiological and instrumentation aspects of this study, and has thus earned the right of principal authorship. Indeed, Dr. Eddington's contributions parallel the development of the cochlear implant project. Many experiments reported here were submitted by him in partial fulfillment of the requirements for his doctorate in biophysics. In 1971 he originally began working with our group as a part-time animal caretaker.

Many problems remain to be overcome, and we can expect technological setbacks. However, I believe society can be assured of the ultimate success of auditory prostheses research for the deaf. Whether this goal is ultimately achieved by our group or by others, is unimportant.

September 1978
Wm. H. Dobelle, PhD
New York, New York

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AUDITORY PROSTHESES RESEARCH WITH MULTIPLE CHANNEL INTRACOCHLEAR STIMULATION IN MAN

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Although single-channel electrode arrays implanted in the scala tympani of deaf patients are useful as an aid to lip reading and for distinguishing some environmental sounds, they do not transmit intelligible speech. However, multichannel electrode arrays, which take advantage of the cochlea's tonotopic organization, may be capable of generating the complex patterns of neural activity necessary for speech discrimination.

In this study, multichannel electrodes were implanted in the cochleas of four volunteers, with access to the connecting wires made through the skin via a percutaneous connector. The major portion of the data presented is from two of these subjects: one has been bilaterally deaf since birth and the other has been unilaterally deaf for 15 years. Preliminary results of experiments with two more recently implanted subjects are described as well as experiments with a fifth volunteer who was implanted with five electrodes by House in 1969.

Data on pitch and loudness discrimination as well as the effects of stimulation parameters on threshold, impedance, and electrode interaction are presented. Place pitch and periodicity pitch were observed in all five volunteers. The results of pitch-matching experiments with the unilaterally deaf volunteer were consistent with tonotopic maps of the cochlea, and experiments indicated that a pitch continuum may be achieved by combining place and periodicity pitch modulation.

Preliminary experiments in tune recognition with one subject demonstrate his ability to recognize simple melodies based on periodicity pitch cues.

These results, coupled with the finding that subjective sensations remain stable over the long-term, support the feasibility of providing artificial hearing with a multichannel cochlear stimulation system.

INTRODUCTION

Between 183,000 to 240,000 individuals in the United States suffer from profound sensorineural hearing loss (greater than 87 dB ISO),[1] which at present cannot be treated. Since histopathological studies have predicted the survival of VIII nerve (based on survival of spiral ganglion cells) in a fraction of the sensorineural deaf,[2] one possible way of restoring hearing to these individuals is to stimulate auditory nerve fibers electrically.

Several groups[3-5] are investigating the feasibility of speech perception with multichannel vibrotactile devices. These devices, which reportedly aid the deaf in lip reading but have not restored the ability to understand speech,[3] have several theoretical advantages. First, because they are noninvasive, they present less risk to the patient. Second, they would be potentially useful to the deaf population as a whole, whereas only the sensory deaf would benefit from a cochlear prosthesis. However, clinical implementation of these simple devices has not been successful because of narrow bandwidth and with difficulty in learning to interpret the converted signals.

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Benjamin Franklin[6] was probably the first to suggest that electricity might be used to produce auditory sensations in the deaf. By 1800 three investigators[7-9] had studied the effects of electrical stimulation on the auditory system with external electrodes. Although the uses of electrical stimulation for otological diagnosis and treatment were investigated sporadically during the 19th and early 20th century,[10,11] direct stimulation of the acoustic nerve was not attempted until 1957, when Djourno and Eyries[12] temporarily implanted an electrode on the VIII nerve of a bilaterally deaf patient during surgery for cholesteatoma. According to this volunteer, the sounds produced by stimulation resembled a spinning roulette wheel or chirping crickets, and the character of these sounds varied, depending on the frequency of stimulation. Although the patient was unable to understand speech, the rhythm of the sounds he perceived reportedly aided him in lipreading.

When Simmons[13] conducted a similar experiment in 1964, the results were so encouraging that he implanted six electrodes in the modiolar VIII nerve tissue of another bilaterally deaf volunteer.[14] Variations in pitch were related to the electrode selected and the frequency of stimulation and the loudness of these sensations depended on stimulation amplitude.

About the same time, House and Urban,[15] House,[16] and Michelson et al[17-19] began investigating the effects of stimulating the acoustic nerve using a single-channel electrode system implanted in the cochlea. Although these devices did not produce recognizable speech, they did provide closer contact with the auditory environment; e.g., patients could detect a ringing doorbell or telephone and read lips more easily. This research also suggested that the cochlea could be stimulated chronically for a number of years without substantial changes in the character of the perceived sounds. House's and Michelson's implants have been the subject of two recent reviews.[16,20]

In 1970, while exploring the feasibility of a visual prosthesis based on electrical stimulation,[21,22] our group began investigating an analogous device[23] based on stimulation of the auditory cortex. Although these initial cortical experiments were encouraging, we decided to shift our emphasis to intracochlear stimulation because the surgery required to implant electrodes in the cochlea was far less drastic. We also decided to concentrate on multichannel devices, which might take advantage of the cochlea's tonotopic organization.

Subsequently, a collaborative program was arranged between the University of Utah and The Ear Research Institute in Los Angeles to investigate the feasibility of these devices. First, however, we reinvestigated House's first patient (C.R., who had been implanted with a five-electrode array), using stimulation equipment[24] developed during our cortical stimulation studies.

The results of our investigations with C.R.[24] were extremely encouraging: 1) place pitch was clearly present, 2) periodicity pitch could be elicited by varying the frequency of stimulation, and 3) C.R. had tolerated a percutaneous connector for five years – which supported our belief that percutaneous connectors should be used in future experimental implants. Keeping all electronic circuitry outside the body would allow precise monitoring of stimuli applied through the electrodes, provide maximum flexibility in terms of stimulus parameters, and eliminate problems of miniaturization and reliability.

We subsequently developed special percutaneous connector-electrode arrays (patients section) and implanted them in two 61-year-old volunteers: J.B., bilaterally deaf since birth, and P.H., unilaterally deaf for 15 years. The information acquired during experiments with these patients forms the basis of this article, and is supplemented by preliminary findings in two more bilaterally deaf volunteers, D.C. and J.S.

EXPERIMENTAL APPROACH

HUMAN VOLUNTEERS

Measurements of basic neural activity tell us little about the perception of complex sounds because the characteristics of neural signals that are important for perception are not understood.[25] Although animal models are useful in assessing some aspects of intracochlear stimulation (particularly those requiring properly timed histological feedback), human subjects are essential to determine whether electrical stimulation is a feasible means of producing recognizable speech perception. Beat frequencies, persistence, and other complex characteristics of sound that must be evaluated subjectively are also difficult to study using laboratory animals. Possible changes in the auditory system related to sensory deprivation that are analogous to those we have observed in experiments on visual cortex[21] would also be difficult to attack in an animal model. Finally, only human subjects can help us determine whether rehabilitation or relearning will be necessary before the device can be used for effective communication.

PERCUTANEOUS CONNECTOR

House and Urban,[15] House,[16] and Michelson et al[17-19] have relied on inductive coupling in which a coil on the outer surface of the skin is coupled electromagnetically to another implanted under the skin. Since minor misalignments of these two coils result in a decrease in signal level to the electrodes, the investigator cannot determine the precise amount of current delivered to the electrodes. This problem can be avoided by implanting the stimulation electronics and using inductive coupling to transmit signals which employ modulation codes to transmit the stimulus parameters rather than using the signal strength itself. But because this approach requires encapsulation of the electronics, unreliability is often a problem.

Inductive coupling and more sophisticated telemetry technology present two even more serious problems: they are inflexible and do not allow monitoring of stimuli at the electrodes. For example, because it is impossible to connect an oscilloscope directly to the stimulation electrodes, one is never certain what stimuli the internal electronics are delivering. In addition to being a disadvantage experimentally, this precludes the experimenter from checking the stimulation equipment for malfunctions such as long-term leakage. The fact that the electronics are implanted also means that the investigator is limited to predetermined stimulation schemes and waveforms. This is especially frustrating during the developmental stages.

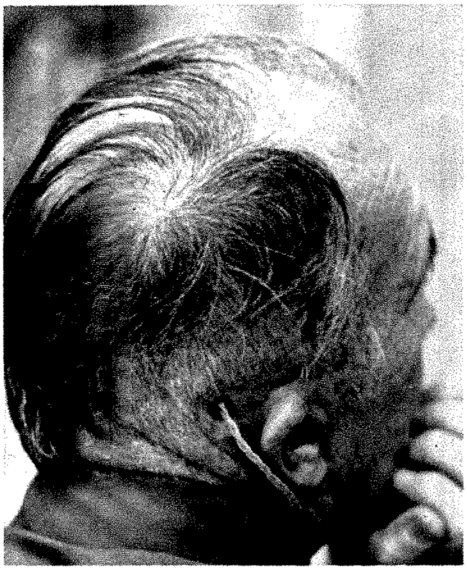

Fig. 1. (J.B.) Photograph of implant several months after implantation. The connecting cable is disconnected from the implant and replaced by a dust cap when experiments are not being conducted. Both J.B. and P.H. have worn these pedestals for 3½ years without infection or other adverse effects.

Percutaneous connectors, on the other hand, allow direct access so voltage and current at the electrode can be measured. They provide complete flexibility in the configurations of electrodes that can be activated, and in the instrumentation that can be used to generate stimuli. And because a percutaneous system involves a minimum amount of implanted hardware and the stimulation equipment can be monitored continually for malfunctions, reliability and safety are greatly enhanced. Our experience with the five patients described here, plus another whose visual

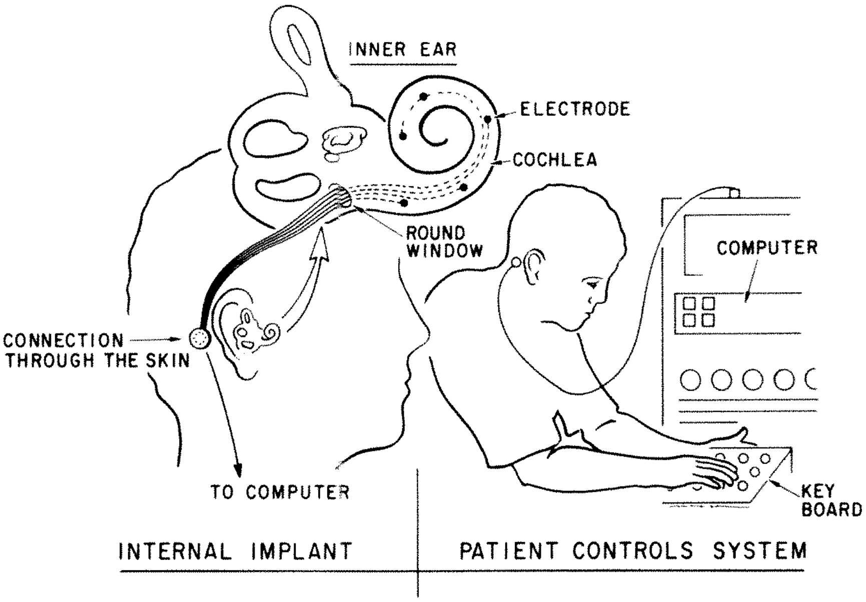

Fig. 2. Patient interacting with the computer-controlled stimulation system. This type of system allows maximum flexibility in the kinds of experiments that can be conducted and, when interfaced with a microphone input, is a complete prototype of an auditory prosthesis.

cortex[26] was implanted with a percutaneous pedestal-connector assembly such as the one shown in Figure 1, has confirmed the feasibility of this approach.

FLEXIBLE EXTERNAL ELECTRONICS

Rather than build generation after generation of electronic stimulation hardware as the techniques of intracochlear stimulation evolve, we use an external computer-controlled stimulation system, which allows us to implement new experiments relatively easily by changing the software rather than the hardware. The system illustrated in Figure 2 provides a versatile test-bed for exploring different methods of stimulation. With the addition of a microphone, this system becomes a complete prototype of an auditory prosthesis, and experiments ranging from signal processing and speech coding to the effects of various stimulus parameters are easily conducted.

QUANTITATIVE APPROACH

Before the effects of stimulus parameters on loudness and pitch can be investigated, it is necessary to lay some preliminary groundwork in terms of the effect of stimulus parameters on more basic characteristics such as perceptual thresholds, electrode impedances, electrode interactions, and general attributes of the subjective sensations produced. This initial work reveals electrical and perceptual sensitivities to various combinations of stimulation parameters.

The loudness of the sensations elicited by stimulation must be predictable if an auditory prosthesis is to prove feasible. Therefore, the relation between stimulus parameters and perceived loudness must be investigated along with questions of dynamic range, difference limens, and adaptation.

Perception of pitch is critically important to the feasibility of artificial hearing by multichannel stimulation. If the placement of electrodes in the tonotopically organized cochlea does not determine the pitch of the sounds elicited, there is little hope that multichannel stimulation will be able to restore the perception of intelligible speech. Thus it is important to determine not only the effect of the stimulation parameters on pitch but, perhaps more important, the effect of electrode placement on pitch.

Once the relationships that control pitch and loudness are known, the problem of generating complex perceptions such as speech can be attacked using vocoder and other digital-processing techniques. It is highly unlikely that this problem could be solved without understanding the relationships of loudness and pitch to the stimulation parameters.

CHOICE OF SCALA TYMPANI

We believe the scala tympani is the location of choice for introducing artificial stimuli through implanted electrodes.

First, the fibers of the VIII nerve are spatially distributed in a predictable tonotopic organization. Second, this area is more accessible surgically than are other more centrally located structures. Third, the scala tympani is accessible through the round window, and electrodes inserted through the round window can be guided along the scala by the bony external boundary. Insertion of electrodes into the scala vestibuli is complicated for two reasons: 1) the sacculi obstruct the placement of electrodes and 2) the electrodes would have to be guided along the delicate Reissner's membrane. When Chouard and McLeod[27] implanted electrodes in the cochlea using a separate fenestration for each one, their initial reports were optimistic. There is insufficient data to assess whether or not this more complicated technique will provide any substantial advantages.

Several other structures have also been proposed as stimulation sites. For example, auditory cortex is the area of choice when dealing with individuals who have degenerated VIII nerves or other more centrally located lesions, and we have stimulated the auditory cortex in several patients while this area was exposed for therapeutic surgery.[23] Simmons[14] implanted electrodes in the modiolus of a deaf volunteer and found that the pitch perceived depended on which electrode was stimulated. The modiolus, however, does not present the easily accessible tonotopic distribution of nerve fibers that is available in the cochlea.

SYSTEMS PHILOSOPHY

In the basic digital signal-processing system we propose, a microphone and analog-to-digital (A/D) converter transform the acoustic input into a digital format for the waveform processing computer. The waveform processing system takes advantage of advanced digital signal processing techniques that suppress noise by filtering and reduce the bandwidth of speech using vocoder techniques.[28] This signal processing section processes the incoming acoustic signal (to suppress noise and reduce bandwidth) and then, based on the relationships between the stimulation modules, specifies the appropriate stimuli for each electrode. To keep the cost of this system at a reasonable level and to increase the chances of developing a portable system, advanced digital signal processing techniques must be complemented by the state-of-the-art, low power consumption, integrated circuit technology which our group has also been involved in developing.[29] A combination of analog and digital methods may be most effective.

PATIENTS AND IMPLANTS

PATIENTS

We believe that the surgical risks of implanting an intracochlear device are minimal when the surgery is done by an experienced otologic surgeon. To minimize risks related to anesthesia, it is desirable to select patients who have already undergone a mastoidectomy with a facial recess approach; in these cases, the necessary bone work has been completed, so the implantation procedure involves local rather than general anesthesia.

After eight years of experience involving electrical stimulation of the human nervous system, we believe that the risks associated with intracochlear stimulation are small. To avoid risks of damaging residual hearing, we have selected volunteers who are profoundly deaf in the implanted ear. Furthermore, we implant only one ear in any individual so that the other ear can benefit from a useful device, providing that one is eventually developed.

Informed Consent. Intensive efforts were made to insure that potential volunteers and their families were fully informed. For example, before signing consent forms, our patients observed mock facial recess surgery in the Ear Research Institute's temporal bone lab. When we were certain that they understood the risks, possible benefits, and experimental procedures, we gave them several months to decide whether they wanted to participate.

To minimize the risk of accidentally instilling false hopes in volunteers, we stressed that the current implants are not designed to be of practical use to them and that they would not be provided with portable stimulation equipment that they could use at home. The volunteers also understood that although they would not be paid for participation, they would be reimbursed for out-of-pocket costs such as transportation. Patients are informed that they may terminate the experiments at any time, and that the implant will be removed at no cost to them.

Recruitment of Volunteers. Many of the criteria for selecting deaf volunteers are obvious. The most important ones are the following:

OTOLOGIC EXAMINATION. The patient's ears must be free of infection, and the tympanic membrane must be intact to minimize the risk of inner-ear infection.

AUDIOMETRIC EXAMINATION. This examination consists of the traditional pure-tone air and bone conduction and speech-detection tests. We also use electrocochleography (ECochG) to make certain that the volunteer is totally deaf in the ear we wish to implant.

NORMAL POLYTOME X-RAYS. Polytome x-rays are taken to determine whether the cochlear structure is normal.

GENERAL PHYSICAL EXAMINATION. All potential volunteers undergo an extensive physical examination to determine whether they are fit for surgery.

EMOTIONAL STABILITY AND ADJUSTMENT. The patient's emotional stability is critically important in terms of gaining his informed consent, assessing his motives for volunteering and ensuring the credibility of experimental results.

COMMUNICATION. Because the experimenter and patient must be able to communicate with one another, bilaterally deaf patients who lip-read well are the most suitable volunteers.

Promontory Screening. Promontory screening is used to determine whether a patient suffers from sensory or neural hearing loss. This procedure, which has been described in detail by House and Brackmann,[30] may or may not elicit sounds in the deaf ear. If it does, the patient is a good prospect to experience some sounds from a cochlear implant. However, the usefulness of this screening procedure is limited because it does not indicate where surviving neurons are located in the cochlea. Although a patient may respond well to promontory stimulation, the surviving excitable tissue may not include the frequency ranges required for speech recognition. This points out the need for an improved screening procedure.

Our peculiarity of promontory stimulation is that nondeaf individuals do not respond. When two members of our group were given a promontory test, neither heard anything; however, one experienced slight disequilibrium at high levels of stimulation.

Otologic History.

C. R. House's first patient,[24] was 69-years-old when we worked with him in June 1974 and is now deceased. He suffered a profound bilateral hearing loss in 1961 because of advanced syphilis. Detailed clinical information on C.R. is presented elsewhere.[15]

J.B. Bilaterally deaf since birth, this 61-year-old mechanical engineer has suffered no subsequent otological diseases

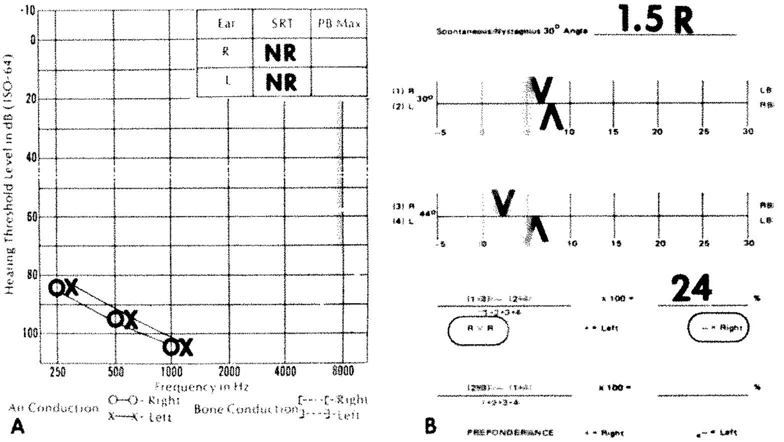

Fig. 3. (J.B.) A) Audiograms showing a profound, bilateral sensorineural hearing loss and no speech discrimination. B) ENG showing slightly reduced vestibular function bilaterally.

and his general health is good. Audiograms and ENG are shown in Figure 3.

P.H. This 61-year-old health inspector became progressively deaf in his left ear after he was stricken with severe Ménière's disease in 1960. Following a number of severe episodes of vestibular vertigo, he was referred for a translabyrinthine vestibular nerve section. Preoperative audiograms (Fig. 4A) showed traces of residual hearing and lack of speech discrimination in his left ear and a high-frequency hearing loss in his right ear. His ENG (Fig. 4B) indicated a total loss of vestibular response in the left ear. In all other respects, this patient was in excellent health.

In 1975, a translabyrinthine nerve section involving removal of the semicircular canals and all vestibular contents was performed on P.H. The vestibular nerve was sectioned, and Scarpa's ganglion was excised without disturbing the facial and cochlear nerves. The bone work for the cochlear implant was also completed at this time. The surgery relieved the patient's vertigo and his

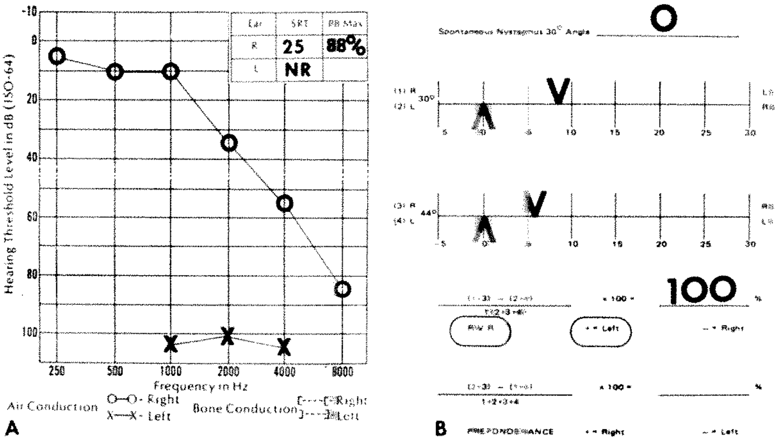

Fig. 4. (P.H.) A) Audiograms indicate traces of residual hearing with virtually no speech discrimination in the left ear and severe high-tone loss with good speech discrimination in the right ear. B) ENG showing a total loss of vestibular response in the left ear.

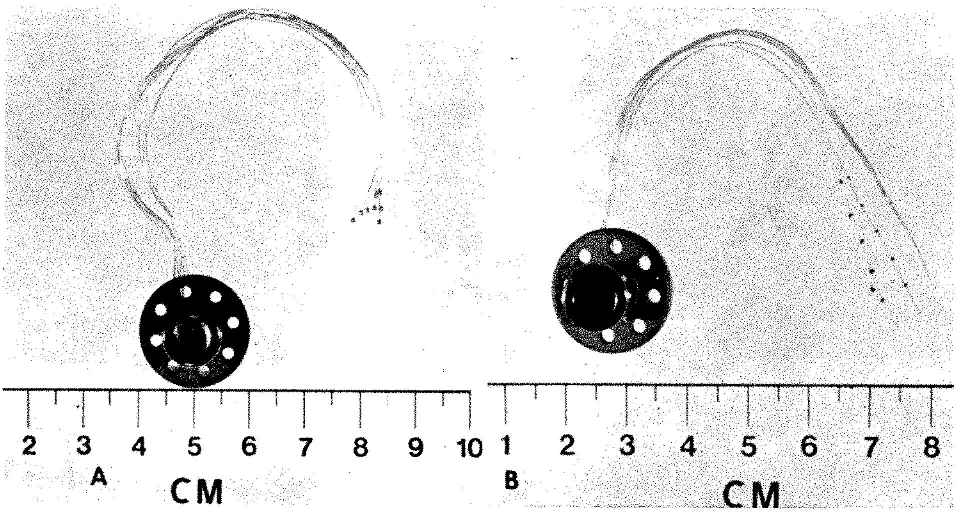

Fig. 5. A) Electrode assembly and percutaneous connector implanted in J.B., D.C., and J.S. Electrodes consist of 0.5 mm platinum balls flamed on 5 mil Teflon®-insulated wire. B) Pedestal and "wrapped" electrode array implanted in P.H. One individual electrode was inserted into the cochlea and acute pitch-matching experiments were then conducted as it was pulled out. The knots of suture material spaced every 5 mm along the electrode wire determined the position of the electrode at different stimulation positions.

response to postoperative promontory tests was satisfactory.

J.S. is a 43-year-old minister who has been afflicted with a progressive bilateral hearing loss of unknown origin for 20 years. Six years ago this condition was aggravated by an undiagnosed infection, and he became profoundly deaf.

D.C., a 47-year-old social worker, became profoundly deaf eight years before surgery as a result of severe Ménière's disease.

PEDESTAL-ELECTRODE ASSEMBLIES

The biological compatibility of the material used to fabricate a cochlear implant is of primary importance. Biological testing in animals has shown that stimulating electrodes made of platinum are biologically acceptable.[23,31-33] Simmons[14] used stainless steel electrodes and noticed large increases in electrode impedance, and this is probably due to the use of this material.[23]

Electrical integrity of the wire insulation is also an important consideration. Pyre-ML® varnish, used by some investigators, is probably not a good choice because it tends to absorb water.[34] We have found that extruded Teflon® insulation not only is biologically compatible but retains its electrical properties in a biological environment. In our work with both cochlear and cortical electrodes,[35] we have found that cleanliness during fabrication is critical.

Because our pedestal-electrode assemblies are made of materials that have different expansion coefficients, sterilization cannot be accomplished by autoclaving. This dictates the use of gas sterilization and extreme precautions to make certain the assembly is properly outgassed. Since we have access to the facilities of a microcircuit lab, we can draw extreme vacuums on the gas-sterilized pedestal-connector assemblies.

C.R.'s electrode bundle consisted of five silver contacts, each about 2 mm^2 in area, spaced approximately 5 mm apart. The silver connecting wires were insulated with Pyre-ML® varnish.[15]

J.B.'s electrode array and pedestal are illustrated in Figure 5A. Each electrode consists of a platinum ball, 1 mm in diameter, formed by flaming the end of 0.5 mil Teflon®-insulated platinum wire. Arrays in D.C. and J.S. were similar.

P.H.'s pedestal and electrode assembly is shown in Figure 5B. This electrode array is in the form of a bundle with electrodes spaced every 4 mm. The longest electrode wire has a 0.5 mm ball flamed to its tip; each subsequent electrode consists of approximately three wraps of uninsulated wire, which encircles the insulated connecting wires of the preceding electrodes. The two single electrodes shown were calibrated every 5 mm for brief pitch-matching experiments in the operating room.

All pedestals except C.R.'s were fabricated of Pyrolized® graphite with a subminiature eight-pin connector glued inside. The electrode wires were crimped to the platinum contacts of this connector, and the entire assembly was attached to the bone with bone screws.

SURGICAL PROCEDURES

Bilaterally Deaf Patients. The details of C.R.'s surgery have been described by House and Urban.[15] In 1975, J.B. underwent implantation surgery. Electrodes 1-6 were placed in the scala tympani through the round window, which was exposed with a facial recess approach under general anesthesia. Because each electrode was inserted individually, the spacing between electrodes was difficult to determine. Electrode 7 was inserted in the bone below the promontory; electrode 8 (the ground electrode) was placed under the temporalis muscle. After the pedestal had been anchored to the mastoid bone with three bone screws, the skin flap of the postauricular incision, which had been punctured with a skin punch, was sutured in place so that part of the pedestal protruded through the skin. The patient was discharged from the hospital two days later, and except for mild disequilibrium lasting several weeks after surgery, he had no major complaints. Postoperative x-rays revealed that the three most apical electrodes (electrodes 1-3) were in contact with one another.

Surgical procedures for D.C. and J.S. were similar to J.B.'s. However, bipolar electrode impedances were monitored to detect shorting, which was avoided. Both patients were discharged from the hospital the morning following surgery.

Unilaterally Deaf Patient. Six weeks after P.H.'s therapeutic surgery, a pedestal-electrode assembly was implanted under local anesthesia. During implantation surgery, an electrode with suture material knotted every 5 mm was inserted approximately 25 mm into the scala tympani through the round window, and acute pitch-matching experiments were conducted as the electrode was pulled out. The bundle was then inserted approximately 18 mm into the scala tympani; unfortunately, because of the bundle's size, electrode 6 did not fit through the round window and remained just outside the cochlea. One of the calibrated electrodes (electrode 7) was placed in the bone below the promontory, and the other (electrode 8) was inserted under the temporalis muscle. The day after surgery, P.H. was discharged and has remained asymptomatic.

STIMULATION EQUIPMENT

As described in the experimental approach section, a computer-controlled stimulation system allows implementation of new experiments by software rather than hardware changes. Thus we have a flexible test-bed for exploring various methods of stimulation, and when a microphone is interfaced to the computer the system becomes a complete prototype of an auditory prosthesis.

DEVELOPMENT OF SPECIFICATIONS

Before designing such a computer-controlled system, the ranges of electrical and acoustical signals it will generate and control must be determined. These determinations were accomplished with manually controlled equipment, which was used in many experiments described in later sections.

Initial Electrical Stimulation Equipment. During acute experiments in the operating room with P.H. and early postoperative experiments with J.B. and P.H., pulsatile stimuli were generated with either a Grass S-88 stimulator and two PSIU-6 constant-current photoisolators or a computer-controlled, optically isolated, constant-current stimula-

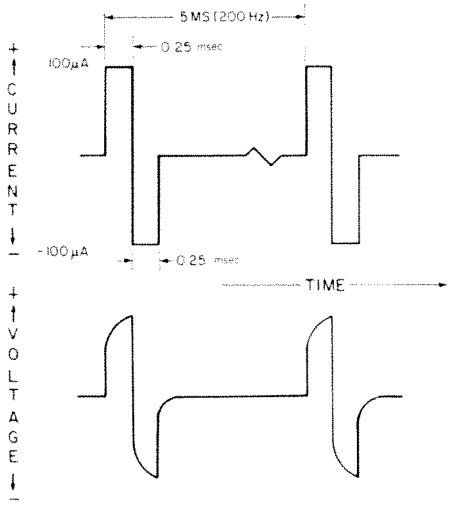

Fig. 6. Typical constant-current biphasic pulsatile waveform with the voltage waveform that is developed across the capacitive impedance.

tor.[36] In later experiments, pulsatile waveforms were also generated by a P6-32 pulse generator (Intercontinental Instruments) and a constant-current photoisolation unit. (There were no differences in the results obtained with the two pieces of equipment.) A Wavetek function generator (Model 136) and constant-current optical isolation unit were used to generate sinusoidal waveforms.

All waveforms were measured with a differential dual-channel oscilloscope (Tektronix No. 565). Current flow was monitored continuously as the voltage drop across a 1000-ohm resistor in series with the output, and stimulus voltage was measured directly across the electrode.

All stimulation equipment was capacitively coupled (0.82 μf capacitor) so that no net charge would be passed. The biphasic stimuli illustrated in Figure 6 were carefully balanced.

The electrode used as ground (temporalis muscle, promontory or 3 x 8 cm arm electrode) made no difference in threshold or perception. Unless otherwise specified, the arm electrode was used as a ground during monopolar stimulation.

Initial Acoustic Stimulation Equipment. A Beltone 15B audiometer and TDH-39 headphones were used to produce the auditory stimuli used for loudness matching. This system was calibrated in sound pressure level (SPL), expressed in decibels relative to 0.0002 dynes/cm^2, with a Bruel and Kjaer 2203 sound-level meter and a Bruel and Kjaer 4151 artificial ear with a type 4132 condensor microphone. The tones used for pitch-matching were generated by a Wavetek function generator (Model 136). All rise-and-fall times of the acoustical bursts were 25 msec in duration.

Resulting System Requirements. Based on experiments conducted with the manually controlled equipment, the following system requirements were determined:

SAFETY. Because access to the implanted electrodes through a percutaneous connector provides a relatively low impedance path into the body, the patient's safety must be carefully considered. The patient, the stimulation electronics, and any equipment with which the patient comes in contact must be isolated from the main 120-V power source. Failure in hardware or software that might allow excessive current leakage to the electrodes must be considered in addition to leakage from the electronic components. The layout, construction, and packaging of the equip-

TABLE 1. TYPICAL RANGES FOR THE PARAMETERS OF PULSATILE COCHLEAR STIMULATION

Parameter	*Typical Parameter*	*Total Range*
Current magnitude	70 μA	0-500 μA
Pulse duration	0.25 msec	0-2 msec
Pulse frequency	200 Hz	Single pulse-800 Hz
Train duration	1.25 sec	0-10 sec

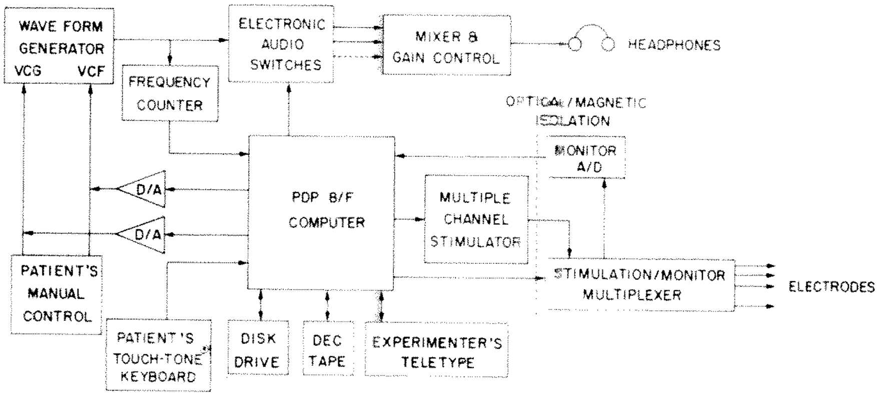

Fig. 7. Block diagram of the computer-controlled stimulation system. The circuitry to the right of the dashed line which is isolated from other parts of the system and from the 120 V ac supply, is powered by two 12 V batteries.

ment should minimize risks such as those caused by spilled water or saline that might compromise patient isolation.

PARAMETERS OF ELECTRICAL STIMULATION. The typical ranges for the parameters of pulsatile stimulation based on previous experiments are shown in Table 1. Because the current amplitudes required during cochlear stimulation are extremely low, special attention should be devoted to reducing noise in the stimulation electronics and connecting cables. The maximum current magnitude of 500 μA and a maximum electrode impedance of 20K ohms, indicates that the stimulation drivers must be able to realize 10 V at their output. This value is well within the range of typical operational amplifiers.

PARAMETERS OF ACOUSTIC STIMULATION. Acoustic stimuli are presented to the normal ear of the unilaterally deaf patient for comparison with the sounds produced by electrical stimulation in his deaf ear. The computer and the patient should be able to control not only the occurrence and duration of these stimuli but also their intensity and frequency. Manual control of the rise and fall times of the acoustic presentation is necessary to produce the desired spectral quality.

ELECTRODE MULTIPLEXING. The system must be able to switch the drivers, isolated ground, and monitor input to any electrode and be easily expanded to cope with larger numbers of implanted electrodes as the technology of electrode fabrication evolves.

DATA LOGGING. To facilitate subsequent retrieval and analysis, all experimental data should be recorded automatically in digital form on some mass storage device as well as in hard-copy form. This allows retrieval, display, and some analysis of the data to be automated.

PATIENT INTERACTION. To automate protocols, the system must be capable of registering the patient's responses to a variety of stimuli. It is also desirable for the patient to control the frequency and intensity of the acoustic presentations during some matching experiments.

OPERATOR INTERACTION. The operator must be able to interact with the system to program the sequence of experiments and enter information such as stimulation parameters that the system will need as the experiment proceeds. A teletype or other alphanumeric display or keyboard is useful because the system can request information and notify the operator about errors in stimulus parameters that exceed safe limits.

AUTOMATED PROTOCOLS. Because this computer-controlled system can register the patient's responses to stimulation through a keyboard, experimental protocols can be automated with appropriate software programs. Program control of experiments saves time, reduces experimenter bias (since the operator does not interact with the patient), and minimizes the risk of injury to the patient by imposing limits on stimulation parameters and electrode configurations.

COMPUTER-CONTROLLED STIMULATION SYSTEM

A block diagram of the computer-controlled stimulator is presented in Figure 7. The system is based on a PDP-8/f computer (12-bit words, 16K words of memory), which is interfaced with three general categories of equipment: 1) circuitry for intracochlear stimulation (stimulation modules, analog-to-digital [A/D] converter, and multiplexer), 2) circuitry for acoustical presentations, and 3) input-output devices such as keyboards, printers, and mass storage devices.

The computer-controlled stimulator diagrammed in Figure 7 has been used during experiments with J.C., P.H., D.C. and J.S. All four volunteers quickly learned how to interact and pace experiments using the Touch-tone® keyboard and feel comfortable about using the system. The system has fulfilled the need for an isolated, multichannel stimulator that automatically sequences experiments and logs data.

FUNDAMENTAL CHARACTERIZATION OF IMPLANT

Most of our detailed data has been obtained from C.R., J.B., and P.H. Preliminary results from the newly implanted subjects, D.C. and J.S., are similar.

SUBJECTIVE SENSATIONS

Pitch. Pitch is determined by the location of the activated electrode in the cochlea (place pitch) and concurrently by the frequency of stimulation (periodicity pitch). Generally speaking, basal electrodes elicit a higher pitch than do apical electrodes. As the frequency of stimulation is increased from 70-800 Hz, the perceived pitch becomes higher. Above 800 Hz, pitch does not seem to change; for this reason, threshold and impedance studies have only been carried out to 800 Hz. Below about 70 Hz, the perceptions begin to flutter and cease to be tonal in character. Pitch perception will be discussed in detail in the pitch perception section.

Loudness. The dominant parameter affecting the loudness of sounds elicited by cochlear stimulation is stimulation amplitude. As amplitude increases (assuming other parameters are constant), loudness also increases. This is also true for increased frequency and pulse duration. These effects are described in the loudness matching section.

Effects of Different Waveforms. Several investigators have reported that different waveforms produce different subjective sensations.[15,18] We presented sinusoidal, triangular, square, and pulsatile waveforms for paired comparisons in the following four sequences: A/B/A, A/A/B, B/A/B, and B/A/A. The patient was instructed to identify which one of the three presentations of a sequence sounded different than the other two. Before comparison, each pair was matched for loudness and pitch. Loudness was matched by adjusting stimulation amplitude; pitch was matched by adjusting the stimulation frequency. We could find no difference in the sensations produced by the four waveforms using the method just described. Thus, in terms of the character of the sound produced, one waveform is no better than any other.

Effects of Electrode Configurations. Certain configurations of electrodes seemed to affect the character of the perceptions. For example, the volunteers stated that sounds elicited by bipolar stimulation were "not as pure" as those elicited by monopolar stimulation. Unfortunately, they were unable to describe these differences more precisely. These differences may be due to the fact that the current amplitudes required to reach threshold during bipolar stimulation were far greater than those required during monopolar stimulation.

The ground used for monopolar stimulation did not affect the character of the sounds perceived. This was true for grounds implanted in the promontory and temporalis muscle as well as for the 3x8 cm ground electrode placed on the ipsilateral arm.

Speech Discrimination

MODULATION AND CARRIERS. When speech was presented to the volunteers using a variety of modulation schemes, their ability to recognize it did not improve. They spontaneously recognized the stimuli as speech when the speech waveform was used to modulate the stimulation amplitude or frequency, or if the speech waveform was applied directly to the electrode. Neither volunteer expressed a preference for any particular modulation scheme.

BANDWIDTH. P.H. stated that high-frequency components of the perception tended to mask the more intelligible portions of the sound he heard. When the speech waveform was low-pass filtered before stimulation, this high-frequency interference was attenuated for cutoff frequencies of 1000-3000 Hz. This did not improve the intelligibility of the perceptions. When high-pass and band-pass filtering were investigated, different bandwidths did not result in any appreciable change in intelligibility.

CONTEXT. If P.H. understood the general context of the conversation and was allowed to watch our lips as we spoke, he recognized isolated phrases. Apparently, the small amount of data transmitted was temporal in character: e.g., when P.H. knew we were saying random numbers between one and ten, the only one he recognized consistently was seven, which consists of two syllables.

Music. When a Bach partita was presented to the volunteers (using the computer to modulate the amplitude and frequency of pulsatile stimuli), both men recognized the sounds as music and could mark the rhythm. They could differentiate between speech and music.

Localization in Space. The sounds perceived by cochlear stimulation were localized within the ear being stimulated. The only exception occurred during matching experiments with P.H., when acoustic tones were presented to his normal ear. In this situation, he merged the acoustic tones heard in his normal ear and the electrical perceptions heard in his deaf ear in "the center" of his head.

Nonacoustic Effects. We doubt that any sensations elicited with electrical stimulation of the cochlea have been electrophonic artifacts, since neither patient's implanted ear produced responses with ECochG.

Because P.H. (the unilaterally deaf patient) has no vestibular function in his implanted ear, it is not surprising that his posture has been unaffected. Similarly, no postural changes have been observed in J.B., D.C. or J.S. since their implantation.

No patients have reported any tinnitus related to the implant or electrical stimulation, and we have not observed any twitching of facial muscles.

Intracochlear stimulation at thresholds lower than 600 μA peak-to-peak has never produced nonacoustic sensations in any patient. Electrodes that do not elicit sounds above this amplitude will cause tickling sensations at higher amplitudes. This is also true of electrodes placed just under the promontory or temporalis muscle.

THRESHOLDS

Method. Thresholds were measured by the descending method. The volunteer was instructed to raise his finger when he heard a sound, and to lower it when the sound ceased. The amplitude of stimulation was set above threshold and each successive stimulation was reduced in steps of 2 μA until the volunteer stopped responding. Each stimulus was presented for 1.5 sec unless otherwise specified; the time between successive stimuli was at least 2 sec. Occasionally, stimulation parameters were such that thresholds were greater than 160 μA peak-to-peak. Under these circumstances, the oscilloscope's resolution required the amplitude to be decreased in steps of 5 μA.

Thresholds of current amplitude measured with the ascending method were consistently 1-2 dB higher than those measured by the descending method because the patient was unfamiliar with the sound he had been asked to

ELECTRODE No.								
1								
2	140							
3	88	192						
4	76	112	240					
5	48	92	144	500				
6	44	80	108	330	f			
7	36	68	120	320	500	f		
8	44	74	120	306	520	f	f	
ARM	44	74	124	290	560	f	f	f
	1	2	3	4	5	6	7	8

A ELECTRODE No.

ELECTRODE No.						
1,2,3						
4	b					
5	b	b				
6	160	180	220			
7 PROMONT	220	b	320	140		
8 MUSCLE	90	88	90	70	100	
ARM	90	84	90	70	100	f
	1,2,3	4	5	6	7	8

B ELECTRODE No.

Fig. 8. A) (P.H.) Thresholds of current amplitude (μA p-p) obtained for all electrode combinations using a biphasic pulsatile waveform. (Stimulation frequency: 200 Hz; pulse duration: 0.25 msec; train length: 1.5 sec). f - Stimulus felt, not heard. B) (J.B.) Same as A. f and b - Stimulus felt, not heard.

detect. If several descending measurements were taken first, to familiarize the subject with the sound, the differences in thresholds obtained using the two methods were not significant.

Monopolar and Bipolar Stimulation. Figure 8 lists biphasic thresholds for all electrode combinations in each patient at stimulation frequencies of 200 Hz, pulse durations of 2.5 msec per phase (positive phase first), and train lengths of 1.5 sec. Note that in the case of P.H. (Fig. 8A), monopolar thresholds could not be obtained for electrodes 6 and 7 because P.H. generally felt the stimuli before he heard the sounds they produced. In P.H.'s case (Fig. 8A) the more apical the electrode, the lower its monopolar amplitude threshold. This suggests that the surviving nerves were located apical to all but electrode 2. This is consistent with data obtained during pitch-matching experiments performed during surgery – when a single wire electrode was inserted into the scala tympani and activated at positions 26, 19, and 6 mm into the cochlea as it was pulled out. P.H. responded at 26 and 19 mm but not at 6 mm, which indicated survival of excitable tissue apical to 19 mm. Thus electrode 4,

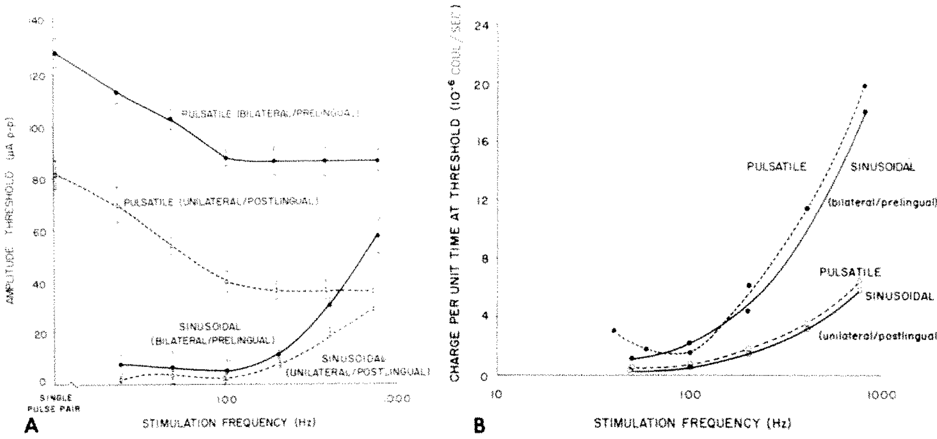

Fig. 9. A) Amplitude threshold versus stimulation frequency for P.H. (unilateral) and J.B. (bilateral). Prelingual and postlingual refer to onset of deafness. Representative electrode 1 is plotted for each patient. The pulse widths for pulsatile stimulation were 0.25 msec; train durations for both sinusoidal and pulsatile stimuli were 1.5 sec. The average number of observations made at each data point was four. B) Data illustrated in A plotted as the charge delivered per unit time at threshold versus stimulation frequency.

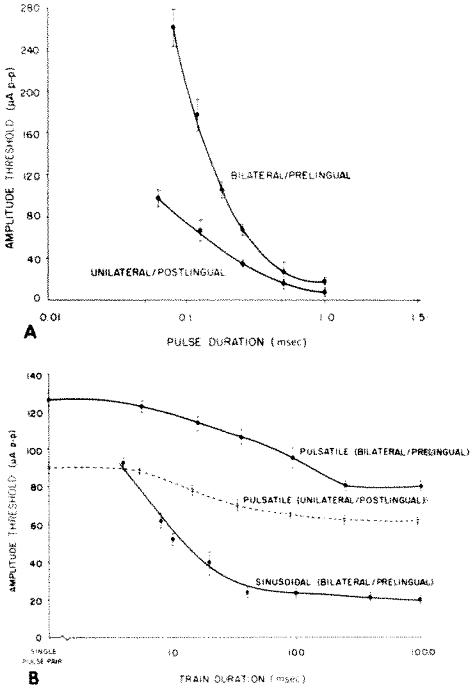

Fig. 10. A) Amplitude threshold versus pulse width for electrode 1 for J.B. (bilateral) and P.H. (unilateral). (Stimulation frequency: 200 Hz; train duration: 1.5 sec). Postlingual and prelingual refer to the onset of deafness. B) Amplitude threshold versus train duration for pulsatile stimulation of electrode 1 in P.H. (unilateral) and J.B. (bilateral). This relationship is also plotted for sinusoidal stimulation in J.B.'s case. (Stimulation frequency: 200 Hz; biphasic pulse width: 0.25 msec.) The smallest sinusoidal train duration plotted is slightly less than one cycle.

which is basal to electrode 1, had to be stimulated at a higher amplitude than electrode 1 to produce the same current density at the nerve mass. Thresholds for bipolar stimulation were usually higher because of the perilymph's shunting effects — especially between adjacent electrodes. As the distance between bipolar electrodes increased, the far-field ground situation was approximated more closely, and thresholds were lower than those of bipolar combinations of adjacent electrodes.

Monophasic and Biphasic Waveforms. Thresholds obtained with monophasic negative stimulation were 4 dB lower than those obtained with biphasic stimulation (positive phase first). Monophasic positive and biphasic thresholds (negative phase first) did not differ significantly from biphasic thresholds (positive phase first).

Stimulation Frequency. In Figure 9A amplitude threshold versus stimulation frequency is plotted for both sinusoidal and pulsatile stimulation. Because the results at all electrodes in each patient are virtually identical, only one representative electrode is plotted for each subject. Note that the thresholds obtained with sinusoidal stimulation were far more sensitive to frequency than those obtained with pulsatile stimulation. The pulsatile threshold decreased as a function of frequency because the charge transferred per unit time increased with fixed pulse width. With the long periods of low-frequency sinusoids, less peak current was required to achieve threshold.

Michelson et al[19] obtained voltage threshold-versus-frequency curves that were identical in shape to those reported here for sinusoidal stimulation. They did not include data on electrode impedance or stimulation current and it is therefore impossible to compare levels of stimulation. However, the relationships between current threshold and frequency that Simmons[14] observed during stimulation of modular VIII nerve were similar to those we observed with C.R.,[24] J.B., P.H., D.C., and J.S.

The fact that both pulsatile and sinusoidal stimulation require more energy to reach threshold as frequency increases has been noted by Simmons.[14] This relationship is illustrated in Figure 9B, where the data in Figure 9A are replotted as coulombs passed per unit time at threshold versus frequency. Note that when expressed in this manner the relationships for pulsatile and sinusoidal stimulation are virtually identical.

Pulse Duration and Train Duration. Figure 10A illustrates the effect of biphasic pulse width on amplitude threshold for a representative electrode from

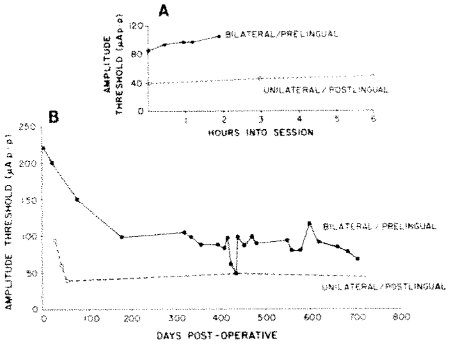

Fig. 11. Thresholds for representative electrode 1 for both P.H. (unilateral) and J.B. (bilateral) during one experimental session using pulsatile stimulation (stimulation frequency: 200 Hz; pulse width: 0.25 msec; train duration: 1.5 sec). B — Long-term thresholds for electrode 1 in J.B.'s and P.H.'s arrays. Note the decrease in threshold for the first three months after surgery. Other variations, except for the drop at 420 postoperative days probably related to the patients' alertness. The stimulation parameters are identical to those noted in (A).

each patient. As pulse width increases, the threshold current decreases because of the increase in charge transferred per unit time.

Amplitude threshold versus train duration for pulsatile stimulation is plotted in Figure 10B for a representative electrode in both patients and for sinusoidal stimulation in J.B.'s case (sinusoidal waveforms were not used with P.H.). The smallest train duration plotted for sinusoidal stimulation represents slightly less than one period; that for pulsatile stimulation represents one pulse pair of the biphasic waveform. Over this range, the pulsatile threshold in J.B.'s case increased by a factor of about 1.6, whereas the sinusoidal threshold increased by a factor of 4.6.

Change With Time. As Figure 11A illustrates, thresholds remained stable over the short-term. For three months after surgery, thresholds dropped significantly in both volunteers as their cochleas recovered from trauma. All other variations – except for the large dip at 420 postoperative days for J.B. – probably can be attributed to variations in the patients' alertness. There is no indication of a rise in threshold, so there is no indication of damage due to stimulation.

ELECTRODE IMPEDANCE

Method. The biphasic pulsatile waveform shown in Figure 6 does not lend itself to a simple definition of impedance because of the complex voltage waveform. In this discussion, impedances for biphasic and sinusoidal waveforms are defined as the ratio of peak-to-peak voltage to peak-to-peak current.

Phase Information. Although impedance is generally characterized by phase and magnitude relationships, generally only magnitude data are described here because the phase relationships of voltage and current were not always recorded. The phase relationships we have measured indicate that angles of −26 to −29° over a frequency range of 22-100 Hz for a sinusoidal stimulation (20 μA, peak-to-peak) are representative. Thus the impedance is capacitive and the current leads the voltage. These results are consistent with simple circuit models developed for electrodes in brain tissue.[37]

Monopolar and Bipolar Stimulation. Figures 12A and B list the impedances for all combinations of electrodes in both patients. Note that all electrodes are continuous. (Electrodes 1, 2, and 3 in J.B.'s array were shorted together.) Impedances for P.H.'s electrodes show an interesting trend (Fig. 12B): they generally increase from right to left and from bottom to top. The data in Figure 12C, which were obtained from an array constructed in the same manner as the one implanted in P.H. and stimulated in saline, suggest that this trend can be explained by the physical characteristics of the electrode array itself. Electrodes 1, 7, and 8 have the largest surface area and, as expected, the smallest impedance. Electrode 2, formed by wrapping uninsulated wire around the insulated wire of electrode 1, has less exposed surface area than electrode 3, which is wrapped around the connecting wires of electrodes 1 and 2. This increase in surface area continues along the bundle to electrode 6, which has the largest surface of the wrapped electrodes because it is wrapped around the connecting wires of electrodes 1-5. This

ELECTRODE No.						
1,2,3						
4	7.8					
5	8.8	11.0				
6	10.8	13.0	13.0			
7	11.2	13.8	13.5	12.5		
8	10.0	13.0	12.8	12.0	10.0	
ARM	7.4	10.0	9.8	9.0	6.9	5.2
	1,2,3	4	5	6	7	8

A ELECTRODE No.

ELECTRODE No.								
1								
2	10.5							
3	8.9	13.0						
4	7.4	11.7	9.3					
5	7.1	11.0	8.8	7.1				
6	8.2	9.8	8.1	8.2	5.5			
7	5.8	9.8	6.9	5.9	5.1	3.9		
8	9.0	11.3	9.5	8.4	7.2	6.2	5.6	
ARM	5.2	9.7	7.1	5.5	4.6	4.1	3.8	4.9
	1	2	3	4	5	6	7	8

B ELECTRODE No.

ELECTRODE No.								
1								
2	1.7							
3	1.5	2.5						
4	1.5	2.2	1.7					
5	1.5	2.2	1.8	1.8				
6	1.2	2.0	1.7	1.6	1.7			
7	1.0	1.7	1.5	1.4	1.5	1.2		
8	1.1	1.7	1.5	1.4	1.5	1.2	1.0	
ARM	0.45	1.2	0.85	0.9	0.9	0.75	0.5	0.5
	1	2	3	4	5	6	7	8

C ELECTRODE No.

ELECTRODE No.							
1							
2	1.6						
3	1.3	2.0					
4	1.4	2.1	1.8				
5	1.4	2.1	1.8	1.8			
6	1.2	2.0	1.6	1.6	1.6		
7	0.95	1.7	1.4	1.4	1.4	1.2	
8	0.95	1.7	1.4	1.4	1.4	1.2	1.0
	1	2	3	4	5	6	7

D ELECTRODE No.

Fig. 12. A) Electrode impedances (in K ohms) for all combinations of stimuli in J.B.'s array. The stimuli were biphasic pulsatile waveforms activated at 20 μA, peak-to-peak (pulse duration: 0.25 msec; train duration: 5.0 sec.) B) Electrode impedances (in K ohms) for all combinations of stimuli in P.H.'s array. Note that impedances increased from right to left and from bottom to top. The stimuli were biphasic pulsatile waveforms activated at 20 μA, peak-to-peak (pulse duration: 0.25 msec; train duration: 5.0 sec). C) Electrode impedances (K ohms) for all combinations of stimuli of a dummy electrode array constructed in the same manner as the one implanted in P.H. Note that this array exhibits the same trend as P.H.'s (see B), which indicates that the trend is related to the array's physical characteristics. Arm in this case indicates a large far field ground electrode (biphasic pulsatile waveforms activated at 20 μA, peak-to-peak; stimulation frequency: 200 Hz; pulse duration: 0.25 msec; train duration: 5.0 sec). D) Estimates of bipolar impedances (K ohms) of the dummy array based on adding the individual monopolar impedances (to the arm electrode) of the electrodes forming the bipolar pair. Note that these approximations and the measured values shown in C form the same pattern. This indicates that bipolar impedances are simply the sum of the monopolar impedance of the two bipolar electrodes.

increase in surface area results in a decrease in the impedance of each electrode measured against the large-area ground.

As shown in Figure 12D, the impedance measured between each electrode pair of the dummy array can be estimated by adding individual impedances measured with the large arm ground. When these approximations are compared with the measured values of P. H.'s electrodes (Fig. 12B), the patterns are identical. Therefore, the impedence patterns of P.H.'s electrodes are due to the electrode array's physical characteristics.

Frequency and Pulse Width. Figure 13A demonstrates how impedance varies with frequency for sinusoidal and pulsatile stimulation. Since the variations are virtually identical from electrode to electrode, only the average for each volunteer is plotted. Impedances produced by pulsatile stimulation were insensitive to frequency, while those produced by sinusoidal stimulation dropped by a factor of 3.5 between 10-1000 Hz.

Figure 13B shows that pulsatile im-

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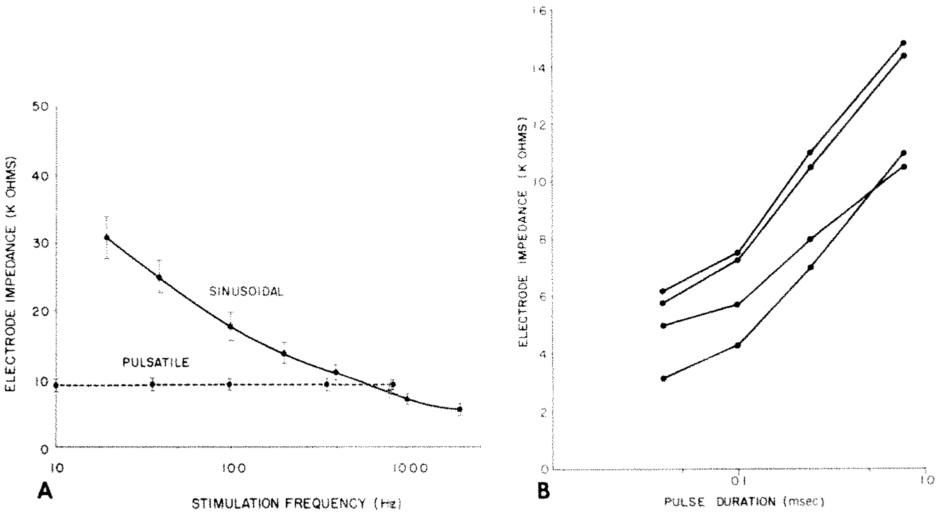


Fig. 13. A) Electrode impedance versus stimulation frequency for sinusoidal and pulsatile stimulation. The averages of all electrodes in each patient are plotted. (Stimulation amplitude; 20 μA, peak-to-peak; pulse width of pulsatile stimuli: 0.25 msec.). B) Electrode impedance versus pulse duration for several of J.B.'s electrodes (stimulation amplitude: 20μA, peak-to-peak; stimulation frequency: 200 Hz). These experiments were not conducted with P.H.

pedances increased as pulse width increased. Since more voltage was required to maintain constant current as the capacitive component of the impedance charged, this is not surprising.

Change With Time. Long-term pulsatile impedances are illustrated in Figure 14. Except for the initial increase and subsequent drop in impedance over the first 100 days postimplantation (possibly caused by proliferation of tissue around the electrodes or recovery from implantation trauma), there seemed to be no significant trends in impedance. The short-term variations were slight in comparison to those that occurred over the long-term.

Stability. Impedance remained constant at peak-to-peak stimulation amplitudes ranging from 1μA (subthreshold) to approximately 250 μA (uncomfortable degree of loudness). Similarly, head position or motion did not affect impedance.

Voltage at Inactive Electrodes. Figure 15A illustrates typical peak-to-peak voltages recorded from all electrode combinations in J.B.'s array while electrode 5 was stimulated at 20 μA (peak-to-peak) using a biphasic waveform. The fact that the voltages of neighboring electrodes measured to ground decreased by a factor of only two or three suggests that interactions may occur between electrodes.

INTERACTIONS BETWEEN ELECTRODES

Electrode interactions were studied in three different ways. The first approach was to discover how an electrode activated at subthreshold currents affected the amplitude thresholds of its neighbors. This effect is called sensitization. The second approach was the same, except that sensitization was measured as the change in stimulation amplitude required to produce maximum comfortable loudness. In the third approach, the patient described the subjective sensations caused by electrode interactions.

Changes in Threshold. Threshold sensitization was investigated by activating a sensitizing electrode with a subthreshold current while finding the threshold of a neighboring test electrode. The results shown in Figure 16A illustrate how the sensitizing current's effect varies, depending on the relative

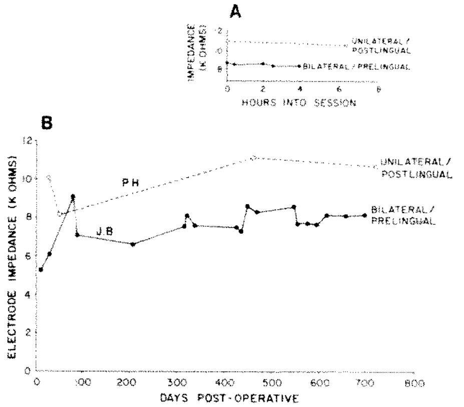


Fig. 14. A) Short-term impedances of electrode 1 for P.H. and J.B. Note that the impedances did not vary significantly during an experimental session. (Stimulation amplitude: 20 μA, peak-to-peak; stimulation frequency: 200 Hz; biphasic pulse duration: 0.25 msec.) B) Long-term impedances for electrode 1 in J.B.'s and P.H.'s arrays. Note the lack of significant trends in the long-term electrode impedance, indicating no damage related to electrical stimulation. Initial variations are probably related to implantation trauma.

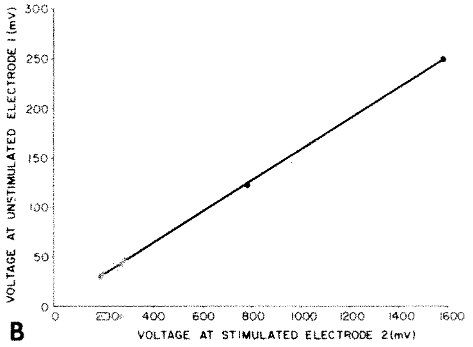
timing or overlap of the two pulses. Since the frequency of stimulation was identical (200 Hz) for both electrodes, the delay ($\triangle$t) was constant for all pulses in the 1.5 sec train. As expected, the maximum effect on the threshold of the test electrode occurred when the pulses of the two stimuli exactly overlapped. When the delay reached twice the pulse duration (0.5 msec in this case) and no overlap occurred, the threshold sensitization was essentially zero.

The fact that no changes in threshold were observed when the simultaneous pulses of two electrodes were interlaced means that a relatively high degree of flexibility exists in minimizing interactions between input channels at the site of cochlear stimulation. Sinusoidal stimulation does not allow such flexibility because interlacing is impossible. For instance, we observed reductions of 17 dB in the sinusoidal amplitude threshold of a test electrode when its neighbor was stimulated sinusoidally just below threshold. House and Urban[15] who generally used sinusoidal stimulation, have reported that threshold sensitization does occur. Simmons[14] observed contrary results with pulsatile stimulation. Our observation that threshold sensitization may or may not occur during simultaneous pulsatile stimulation — depending on the amount of pulse overlap — but always occurred during sinusoidal stimulation, may explain House's and Simmons' conflicting reports.

Changes in Maximum Comfortable Listening Level. The overlap effects seen in threshold sensitization were also manifested as variations in the loudness of maximum comfortable listening level. Figure 16B illustrates these effects for two typical electrode pairs. The pair in which electrode 3 was the sensitizing

ELECTRODE No.	1,2,3	4	5	6	7	8
1,2,3						
4	0.003					
5	0.0112	0.011				
6	0.030	0.033	0.058			
7	0.057	0.060	0.070	0.027		
8	0.066	0.069	0.078	0.037	0.0095	
ARM	0.084	0.086	0.195	0.055	0.05	0.016

A ELECTRODE No.



B

Fig. 15. A) (J.B.) Voltages (peak-to-peak) measured at all electrode combinations in electrode array while electrode 5 was stimulating monopolarly with a biphasic waveform (stimulation frequency: 200 Hz; pulse width: 0.25 msec; stimulation amplitude: 20 μA, peak-to-peak). B) (P.H.) The voltage measured between nonactivated electrode 1 and the far-field arm electrode during monopolar stimulation with electrode 2.

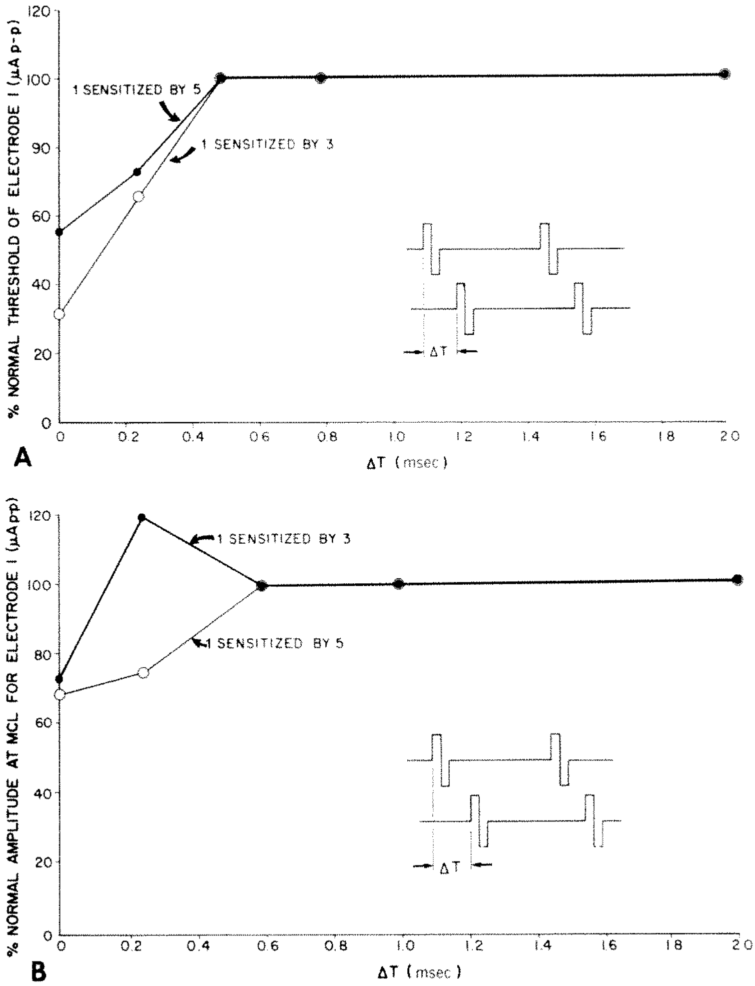


Fig. 16. A) Interactions between simultaneously stimulated electrodes. These interactions are presented in terms of how the threshold of the test electrode is influenced (as the percentage of normal threshold) by another electrode stimulated subthreshold (80% of threshold). This data is plotted as a function of the delay between the onset of the two biphasic stimuli (stimulation frequency: 200 Hz; pulse width; 0.25 msec). B) This figure plots data obtained under the conditions described in (A). However, the influence of the subthreshold electrode is presented as the amplitude at the test electrode required to elicit the loudest sensation that is still considered comfortable (MCL — Maximum comfortable listening level).

electrode exhibited a unique property: the test electrode (electrode 5) was maximally desensitized when the delay was equal to one pulse duration. This desensitization was probably caused by the following: when two adjacent electrodes have different polarities, the active electrode at the lower potential may act as a ground or return path for the electrode at the higher potential, shunting current through the perilymph and away from excitable neural tissue. Why this desensitization was not observed with all electrode pairs is unknown.

Changes in Subjective Sensations. The effects of stimulating two electrodes simultaneously with suprathreshold currents were divided into interlaced and noninterlaced pulses. Interlacing was accomplished by stimulating one electrode at a frequency that was some integral multiple of the second electrode's stimulation frequency. In the noninterlaced or asynchronous case, pairs of activated electrodes were stimulated at frequencies that were not integral multiples. In this case the pulse pairs of the two activated electrodes overlapped in time at a frequency equal to the difference between the stimulation frequencies at each pair of electrodes.

If the pitch perceptions elicited by stimulating each electrode separately were markedly different, the patient usually heard two separate sounds for simultaneous stimulation (interlaced or asynchronous). If, however, the two sounds did not differ markedly in pitch, he perceived only one sound. These results agree with those of House[16] and Simmons.[14]

During asynchronous stimulation, loudness was modulated at the beat frequency (the difference between the two stimulation frequencies); during interlaced stimulation, loudness remained constant. Modulation of loudness could also be elicited when only one of the two electrodes was activated above threshold. Loudness increased only when the stimulation pulses of the two electrodes overlapped in time. Generally, when the patient heard two pitches at the same time, the loudness of only one of the sounds was modulated.

CURRENT SPREAD IN THE COCHLEA

One way to minimize interactions produced by simultaneous stimulation is to minimize the current spread by bipolar stimulation of two adjacent electrodes rather than by monopolar stimulation with a far-field ground. In general, bipolar stimulation of adjacent electrodes restricts the flow of current to a greater degree than does monopolar stimulation; the current flows between the two adjacent electrodes rather than from the intracochlear electrode to the ground placed on the patient's arm. In fact, Merzenich and his colleagues[38-40] experimented in cats using bipolar electrodes (70-90 μm in diameter with 0.4-1.1 mm spacing and mounted in a Silastic® package molded to fill the scala tympani). By recording single-unit responses in the central nucleus of the ipsilateral inferior colliculus in cats implanted with these electrodes, Merzenich[illegible] was able to determine the voltage required at his bipolar electrode to excite fibers at various distances from the electrode. For instance, using a pair of bipolar electrodes centered in the 10 kHz section of the cochlea, he found that the stimulus voltage required to excite a unit with a characteristic frequency of about 5.7 kHz (4 mm from the 10 kHz position in cochlear distance) was about 10 dB (or 3.2 times) greater than that needed to excite a unit of 10 kHz directly under the electrode pair.

Although we have not tested our electrodes on animals in this manner, an analysis of the voltages that appeared at unstimulated electrode 1 in P.H.'s array during stimulation with electrode 2 (his electrodes were spaced 4 mm apart) provides some insight into the subject. For example, the amplitude threshold and impedance data for electrode 1 indicate that 440 mV (peak-to-peak) is needed at electrode 1 before it will reach threshold. By referring to the relationship in Figure 15B, which gives the voltage measured at electrode 1 as a function of the voltage at activated electrode 2, we see that electrode 2 must be stimulated at 1.4 V (peak-to-peak) to bring electrode 1 to its threshold voltage. This is 7.6 dB, or 2.4 times greater than the 600 mV needed to reach threshold at electrode 2.

Although the current localization obtained with our electrodes was only 75% as good as that achieved by Merzenich,[40] this was probably sufficient because, even when P.H.'s electrode 2 was activated at an amplitude that elicited maximum comfortable loudness (2.3 threshold), it would not generate the necessary 440 mV (peak-to-peak) needed at electrode 1 for the latter to reach threshold. The good electrical separation for monopolar stimulation with P.H.'s electrode array is probably related to the fact that the array did not displace the perilymph, and thus fluid formed a path of low resistance shunting current away from excitable tissue which was not adjacent to the elec-

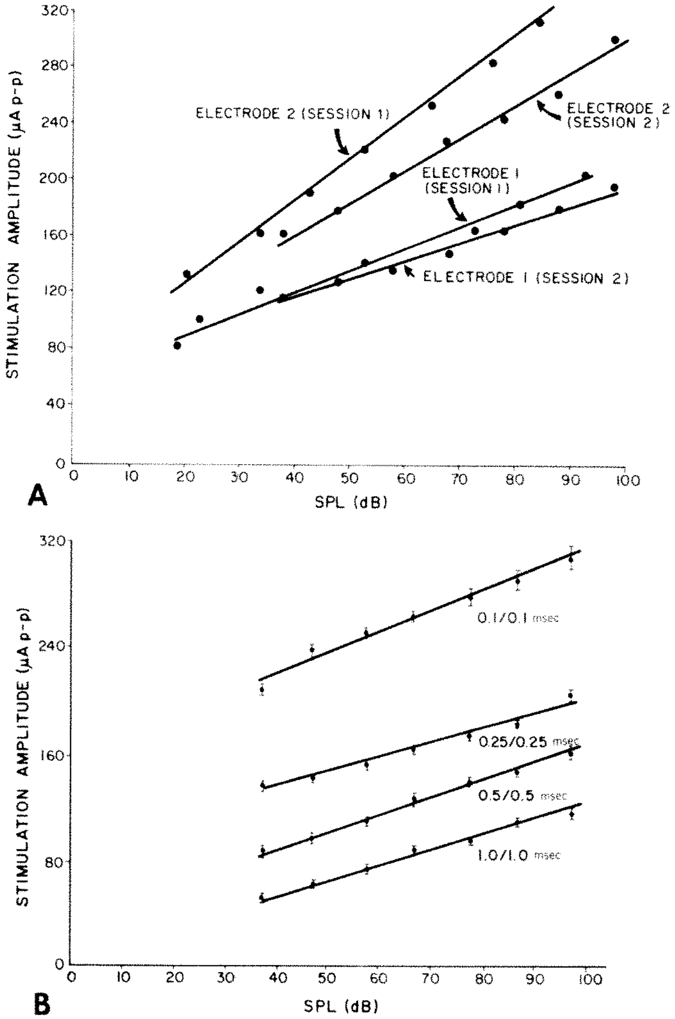


Fig. 17. A) Relationship of stimulation amplitude (uA, peak-to-peak) and perceived loudness (dB SPL) for biphasic, constant-current stimulation of P.H.'s electrodes 1 and 2 (stimulation frequency: 200 Hz; pulse duration: 0.25 msec). The straight lines generated by the method of least squares are the best fit. The values plotted represent averaged data; the average number of observations for each point is four. B) Stimulation amplitude plotted as a function of perceived loudness for four pulse widths: 0.1 msec/0.1 msec, 0.25 msec/0.25 msec, 0.5 msec/0.5 msec, and 1.0 msec/1.0 msec. The frequency of stimulation was held constant at 200 Hz.

trode. Another possible explanation involves neuronal inhibitory effects, which may "sharpen" the subjective sensations.

LOUDNESS MATCHING

EXPERIMENTS WITH UNILATERALLY DEAF VOLUNTEER

Method. In 1976 two loudness-matching experiments were conducted with P.H. The sessions were held six months apart, and each lasted several days. During the experiments, P.H. sat in an acoustic booth (IAC 430); all equipment, except for the headphones, was located outside the booth. A tone of 1.5 kHz was used as the standard auditory stimulus; according to P.H., this tone most closely approximated the pitch of the perceptions elicited by electrodes 1 and 2. During the first session, the range of intensity over which matching was done was 18-90 dB SPL. But because P.H. had difficulty matching lower level stimuli, the range was changed to 38-98 dB SPL

TABLE 2. LEAST-SQUARES REGRESSION COEFFICIENT, 95% CONFIDENCE LIMITS AND CORRELATION COEFFICIENTS FOR DATA SHOWN IN FIGURE 17A

Electrode Number	*Session Number*	*Least-squares Regression Coefficients*		*95% Confidence Limits for Slope*	*Correlation Coefficient*
		Slope	*Intercept*		
1	1	0.764	28.3	± .00250	.939
1	2	0.626	32.7	± .00276	.987
2	1	1.16	33.9	± .02380	.995
2	2	1.48	32.6	± .01250	.994

during the second session. Cochlear stimuli were always biphasic, pulsatile waveforms.

Loudness-matching experiments using procedures derived from the three classical psychophysical methods are all sensitive to experimentally induced biases. The Method of Constant Stimuli is probably the most risky in this respect.[41] We chose the Method of Limits because, unlike the Method of Adjustment, it does not require the patient to come in contact with any of the electrical equipment except the headphones. Amplitudes of the cochlear (comparison) stimuli were varied in steps of 2 μA until P.H. indicated that the loudness of the tone produced in his deaf ear by the comparison stimulus matched the one produced in his normal ear by the standard stimulus. Starting amplitudes of comparison stimuli were randomized in both ascending and descending trials. Each acoustic stimulus was presented for 2 sec (25 msec rise/delay time) and was followed 1.5-2 sec later by the electrical cochlear stimulus. At least 2 sec elapsed between trials.

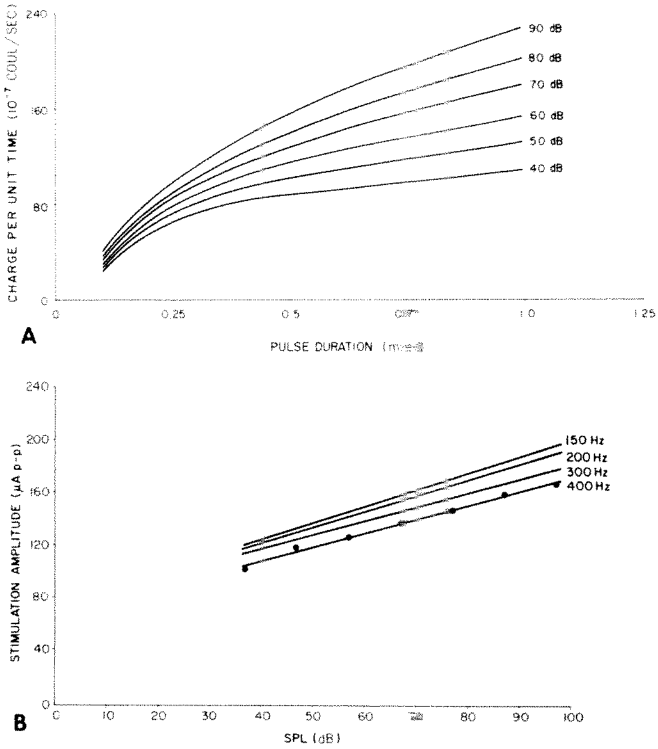


Fig. 18. A) Constant loudness contours as a function of charge delivered per unit time and pulse duration (stimulation frequency: 200 Hz). B) Stimulation amplitude versus perceived loudness at four different stimulation frequencies: 150 Hz, 200 Hz, 300 Hz, and 400 Hz. In the case of 400 Hz, averaged data are also plotted. These data are typical of the scatter obtained at the other frequencies. (Biphasic pulsatile stimulation with pulse durations of 0.25 msec was used.)

Because the effects of temporal summation, adaptation, and enhancement often affect a patient's perception of comparison tones, the sequence and timing of presentation are extremely important when matching loudness. Since we used delayed matching with interburst delays of 1.5 to 2 sec and durations of 2 sec it was unlikely that a significant degree of bias was introduced by summation, enhancement or adaptation effects.[41-60]

Data Obtained.

EFFECT OF STIMULATION AMPLITUDE. The effect of pulsatile stimulation amplitude on perceived loudness is illustrated in Figure 17A, which summarizes loudness-matching data obtained during both stimulation sessions. The least-squares regression coefficients, correlation coefficients, and 95% confidence limits for the slopes of the straightline approximations are shown in Table 2. These data indicate that perceived loudness, when expressed in dB SPL, increased linearly with electrical stimulation amplitude. The change in the slope of this relationship for both electrodes between the first and second stimulation sessions reflects the reduction in dynamic range and threshold over nine months. The small dynamic range of the current amplitude is consistent with data obtained with animals.[25]

EFFECT OF PULSE DURATION. As illustrated in Figure 17B, if stimulation amplitude and frequency remain constant, an increase in pulse width results in increased loudness. This is not surprising because an increase in pulse width (other parameters remaining constant) represents an increase in charge delivered per unit time. Figure 18A, which plots equal loudness contours for charge per unit time versus pulse duration, illustrates that an increase in pulse duration results in concomitant increase in the charge per unit time required to maintain constant loudness.

EFFECT OF STIMULATION FREQUENCY. The effects of the frequency of stimulation on perceived loudness are illustrated in Figure 18B. These data show that to maintain the same loudness, the amplitude of intracochlear stimulation must be increased when the frequency of stimulation is decreased, because reducing the frequency while keeping the amplitude constant results in a decreased charge delivered per unit time. These results conflict with those obtained by Simmons[14] during the stimulation of modiolar VIII nerve. In Figure 19A, the same data are plotted as contours of equal loudness for charge delivered per unit time versus frequency of stimulation. This representation emphasizes that an increase in charge delivered per unit time is required to maintain constant loudness when the stimulation frequency is increased, even though the amplitude of stimulation decreases.

Expression for Relating Stimulation Parameters and Perceived Loudness. The relationships shown in Figure 19A allowed us to select the required charge to be delivered per unit time to electrode 1 needed to produce perceptions of specified loudness for stimulation frequencies between 150-400 Hz. In the case of computer-controlled stimulation, however, it is desirable to express this information in the form of an equation that can be incorporated into the stimulation software. For example, when comparing the pitch of sounds elicited by different frequencies, the sounds could be adjusted automatically to the same loudness using this equation.

The general straight-line expression of the constant loudness contours illustrated in Figure 19A relates the charge delivered per unit time (Q/t) to loudness (SPL) and frequency (f) is:

Equation 1

$$Q/t = \text{YINT} + \text{slope } f,$$

where YINT represents the y intercept for the specific loudness contour.

Note in Figure 19A that the slope and YINT of the contours increase as SPL increases. This relationship, when plotted in Figure 19B, indicates that both the slope and YINT increase linearly with SPL; i.e., both can be related to SPL by using the following straight-line equations:

Equation 2

$$\text{Slope} = a_1 + b_1 \cdot \text{SPL and}$$

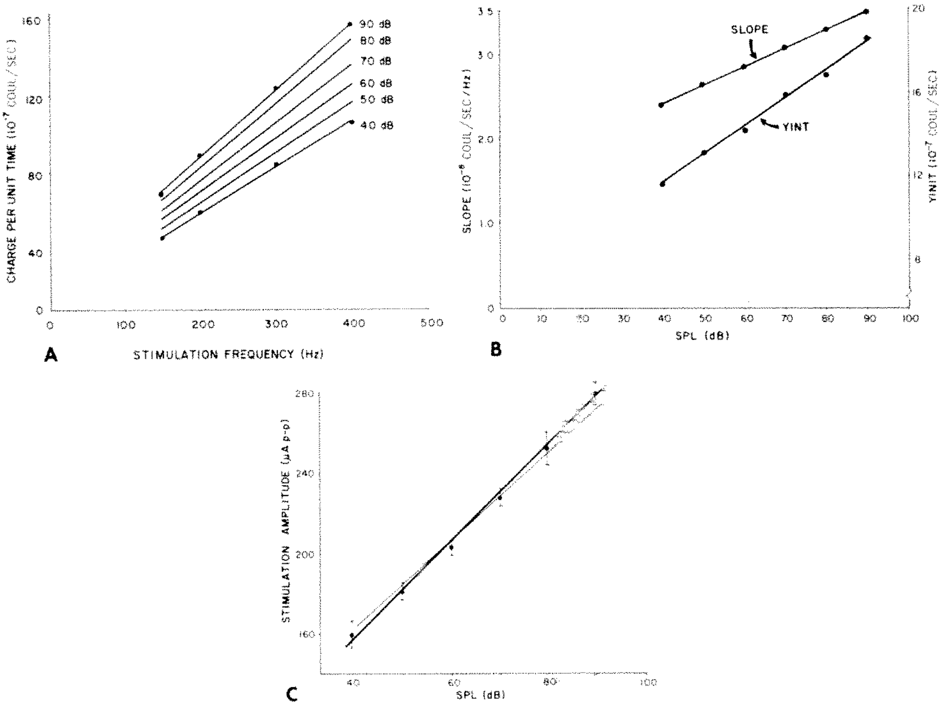


Fig. 19. A) The data shown in Fig. 18B, replotted as contours of constant loudness as a function of charge delivered per unit time (Q/t) in coulombs per sec (stimulation frequency: 200 Hz). The scatter is illustrated by the contours of the data obtained at 90 and 40 dB. B) The slope and y intercept (YINT) of the constant loudness contours of (A) plotted as a function of SPL. Note the linear relationship of these parameters. The scales for slope and YINT are the left and right ordinates, respectively. C) Comparison of the relationship between stimulation amplitude and perceived loudness (as predicted by equation 7 for electrode 2) and the relationship obtained from a least-squares straight-line fit of the loudness-matching data obtained for electrode 2 during the second experimental session. The darker line and standard deviations correspond to measured data, and the thin line to the prediction.

Equation 3

$$\mathrm{YINC} = a_2 + b_2 \cdot \mathrm{SPL},$$

where $a_1 = 1.54 \times 10^{-8} \dfrac{\mathrm{coul/sec}}{\mathrm{Hz}}$; $b_1 = 2.15 \times 10^{-10} \dfrac{\mathrm{coul/sec}}{\mathrm{Hz} \cdot \mathrm{SPL}}$; $a_2 = 6.54 \times 10^{-7}$ coul/sec; and $b_2 = 1.33 \times 10^{-8} \dfrac{\mathrm{coul/sec}}{\mathrm{SPL}}$.

Because equations 2 and 3 provide the slope and YINT for any loudness (SPL) in the range of interest, these expressions can be substituted for the coefficients (slope and YINT) of equation 1 to produce equation 4, which is the general expression for relating charge delivered per unit time to SPL and frequency:

Equation 4

$$Q/t = a_2 + b_2 \cdot \mathrm{SPL} + (a_1 + b_1 \cdot \mathrm{SPL}) \cdot f.$$

Charge per unit time can be expressed in terms of the zero to peak stimulation amplitude (A) for symmetric biphasic stimulation as:

Equation 5

$$Q/t = A \cdot f \cdot 0.5 \text{ msec},$$

where 0.5 msec is derived from the total pulse width (0.25 msec/0.25 msec) of the biphasic stimulus.

Substituting equation 5 for the left side of equation 4 and solving for A yields equation 6, which is the transform that provides the stimulation amplitude needed at electrode 1 to produce perceptions of specific loudness between 30-100 dB SPL at any stimulation frequency between 100-400 Hz:

Equation 6

$$A = \frac{a_2 + b_2 \cdot SPL}{f \cdot 0.5\,\text{msec}} + \frac{a_1 + b_1 \cdot SPL}{0.5\,\text{msec}}.$$

By normalizing this equation with respect to the dynamic range (over which the matching data were taken) of electrode 1, so that the stimulation amplitude is represented as the percentage of the electrode's dynamic range rather than as an absolute amplitude, it is possible to determine whether the expression can be generalized to include electrode 2. This normalized equation yields:

Equation 7

$$\%\ \text{Dynamic Range} = \frac{A-L}{H-L},$$

in which L represents the stimulation amplitude producing the softest sound (59.2 μA in the case of electrode 1) and H represents the stimulation amplitude eliciting the loudest sound (96.7 μA for electrode 1).

In Figure 19C, the relationship between the stimulation amplitude and perceived loudness predicted for electrode 2 by equation 7 is plotted with the straight-line fit (least-squares) of the actual matching data taken for this electrode during session two (Fig. 17A). The close correspondence of these two relationships indicates that equation 6 can be extended to electrode 2 if the expression relating stimulating amplitude to loudness and stimulation frequency is normalized for dynamic range.

It can be argued that it is possible to generalize equation 7 to include both electrodes because they might stimulate the same mass of nervous tissue. However, initial pitch-matching experiments indicated that because each electrode elicited a different pitch, each was stimulating a different nerve population. At 200 Hz, for example, electrode 1 elicited a sound that corresponded most closely to a tone of approximately 1300 Hz, whereas electrode 2 elicited a sound corresponding to a tone of approximately 1600 Hz. This pitch-matching information suggests that the two electrodes did indeed stimulate different segments of excitable tissue and that the relationship of loudness, stimulation amplitude, and frequency — when normalized for dynamic range — could be generalized for two electrodes stimulating different excitable tissue.

RELATIVE AND ABSOLUTE DATA

Dynamic Range. Previous investigators have measured the total dynamic range of stimulation amplitude, i.e., the range of magnitude between tones that are barely perceptible (threshold) and those that are uncomfortably loud, with bilaterally deaf volunteers. For instance, Simmons[14] reported dynamic ranges of 15-25 dB (over different electrodes; referenced to threshold) during stimulation of modiolar VIII nerve. Michelson[17-19] and House[15,16] reported dynamic ranges of 8-30 dB and 4-16 dB, respectively, during cochlear stimulation using sinusoidal waveforms. During experiments with C.R.,[24] we observed dynamic ranges of 6-13 dB with pulsatile stimulation. In the experiments described here, we recorded dynamic ranges of 12-15 dB during sinusoidal stimulation and 5-7 dB during pulsatile stimulation. These dynamic ranges were constant with stimulation frequency and remained so over the long term.

Difference Limens. Difference limens for stimulation amplitude, measured by presenting A/B comparisons with the patient indicating same or different, were approximately −28 dB, relative to the stimulus amplitude at which they were measured. This difference limen translates into 2-5 μA. In P.H.'s case, the difference limen for amplitude stimulation translates to approximately 3 dB SPL.

Adaptation and Persistence. Both P. H. and J.B. reported that their perceptions accommodated with time while stimulation remained constant. According to J.B., the loudness of the sounds began to drop substantially about 40 sec after the onset of stimulation. This information was consistent with the results of loudness-matching experiments conducted with P.H., who reported that loudness remained constant at 50 dB SPL for 2 sec after the onset of stimulation, dropped to 40 dB at 60 sec, and dropped to 30 dB after a total of five

TABLE 3. SUMMARY OF ALL POSSIBLE A/B PITCH COMPARISONS FOR C.R.*

Electrode Stimulated First	*Electrode Stimulated Second* 1	2	3	4	5
1	— —	13 100%	7 100%	2 100%	5 100%
2	7 100%	— —	14 86%	10 100%	5 100%
3	4 100%	13 85%	— —	13 77%	7 86%
4	2 100%	9 89%	17 59%	— —	16 94%
5	5 100%	2 100%	6 77%	20 70%	— —

*The number of trials and the percentage of responses that correlated with cochlear position are given for each possible presentation sequence. The biphasic stimulation was at 200 Hz with pulse durations of 0.2 msec. Of a total of 177 presentations, 86% correlated with the tonotopic organization of the cochlea. (Redrawn from Mladejovsky et al[24].)

minutes. It was also consistent with similar accommodation effects we observed during stimulation of visual[21,22] and auditory[23] cortex. This effect can be overcome by using interrupted trains of stimuli.

In visual studies we have demonstrated that phosphenes (tiny dots of light elicited in the blind when primary visual cortex is stimulated) can persist after extremely high stimulation amplitudes.[21,22] This effect has not been observed during intracochlear stimulation, however.

PITCH PERCEPTION

BASIC CONCEPTS

It is important to differentiate at the outset between acoustic stimulation frequency, electrical stimulation frequency, and perceived pitch. An individual with normal hearing associates a pitch with an acoustic frequency; sometimes the terms are mistakenly used synonymously. Because of the relatively close relationship between a sound's pitch and acoustic frequency, this same relation is sometimes erroneously applied to the relationship between electrical stimulation frequency and perceived pitch. When an intracochlear electrode is activated at a frequency of 400 Hz, a subject will not necessarily perceive a pitch that one would associate with an acoustic frequency of 400 Hz.

The relationships between the parameters of intracochlear stimulation and perceived pitch can be expressed in relative or absolute terms. When working with a bilaterally deaf volunteer, only relative information is available because the patient can only describe a pitch by comparing it with that of a previous percept. A unilaterally deaf volunteer on the other hand, can provide absolute information by matching the pitch of the sound elicited by electrical stimulation in his deaf ear with that of an acoustic tone he hears in his good ear.

RELATIVE DATA OBTAINED FROM BILATERALLY DEAF PATIENTS

The data reported here were obtained during experiments conducted with three bilaterally deaf patients: C.R.[15] and D.C.,[61] who were deafened postlingually, and J.B., who was deafened prelingually.

Place Pitch. The tonotopic organization of the cochlea suggests that the pitch of perceptions elicited by intracochlear stimulation depends on the position of electrodes in the cochlea; i.e., an apical electrode should produce a lower pitch than does a more basal electrode. The results of House and Urban's initial experiments with C.R.[15] suggest that this assumption may be true.

TABLE 4. SUMMARY OF ALL POSSIBLE A/B PITCH COMPARISONS FOR J.B.*

Electrode Stimulated First	*Electrode Stimulated Second*			
	1,2,3	*4*	*5*	*6*
1,2,3	— —	5 Same	7 100%	8 88%
4	4 Same	— —	3 Same	9 78%
5	6 100%	4 Same	— —	5 Same
6	11 91%	8 75%	4 Same	— —

*The stimulation parameters used in this experiment were identical to those listed in Table 3, except the pulse duration was 0.25 msec. A comparison of Tables 3 and 4 indicates that place-pitch discrimination was far more difficult for J.B. than for C.R. Of the 74 presentations, 58% correlated with the cochlea's tonotopic organization. ("Same" means that J.B. always described the two sounds as having the same pitch.)

Several years after House's initial observation of place pitch, we reinvestigated C.R. to confirm the existence of this phenomenon.[24] We tested for place pitch by sequentially stimulating two different electrodes at the same pulsatile stimulation frequency for approximately 1 sec each and asked C.R. to report the relative pitch. If his responses were consistent with the cochlea's tonotopic organization (i.e., if the most basal of the two electrodes produced the higher pitch), they were considered correct. The order in which the electrodes of each pair were activated was randomized and all possible pair combinations were investigated. The results of 177 trials are presented in Table 3; note that 86% of the patient's responses were correct. Adjacent electrodes elicited the lowest percentage of correct responses, while all electrode pairs that were separated by two or more inactive electrodes elicited 100% correct responses.

Experiments with J.B. conducted in the same manner produced similar results (Table 4), but J.B., who has been deaf from birth, had more difficulty distinguishing differences in pitch between adjacent electrodes than did C.R. J.B. maintained that, in general, the pitch of sounds elicited by adjacent electrodes was the same. This difference may be related to the fact that whereas J.B. was prelingually deafened, C.R. had acquired his deafness postlingually.

Results from our most recent experiments with patient D.C.,[61] conducted using the same method as that used with C.R. and J.B., are given in Table 5. These data clearly demonstrate that the relative pitch elicited by electrical stimulation at a constant stimulation frequency varies consistently with the ton-

TABLE 5. SUMMARY OF ALL POSSIBLE A/B PITCH COMPARISONS FOR D.C.*

Electrode Stimulated First	*Electrode Stimulated Second*					
	1	*2*	*3*	*4*	*5*	*6*
1	—	5 100%	5 100%	5 100%	5 100%	5 100%
2	5 100%	—	5 100%	5 100%	5 100%	5 100%
3	5 100%	5 100%	—	5 100%	5 100%	5 100%
4	5 100%	5 100%	5 100%	—	5 100%	5 100%
5	5 100%	5 80%	5 100%	5 100%	—	5 100%
6	5 100%	5 100%	5 100%	5 100%	5 100%	—

*The stimulation parameters and method used were the same as in Table 4. There were 5 presentations for each combination. The average percent correct for all of the 150 trials was 99.3%. (Redrawn from Eddington et al[61].)

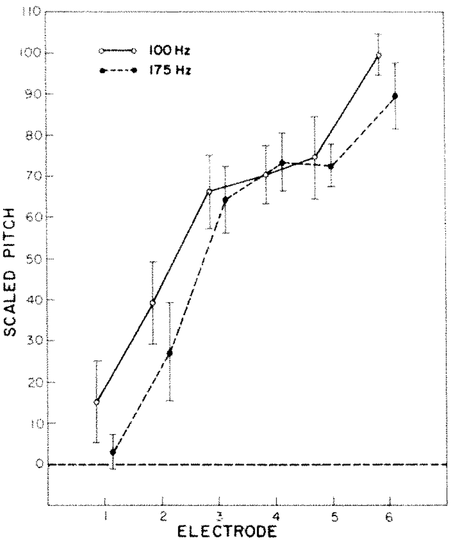


Fig. 20. (D.C.) Pitch scaling results for stimulation at frequencies of 100 Hz and 175 Hz at all six intracochlear electrodes. Notice the trend of pitch to increase with increasing distance from the apex and increasing stimulation frequency.

otopic placement of the electrodes. Similar results have been obtained with J.S.

Periodicity Pitch. Periodicity pitch modulation refers to changes in pitch caused by varying the stimulation frequency. As frequency increases from 80-800 Hz, the perceived pitch becomes higher. This is consistent with pitch-scaling experiments conducted with single channel implants by Michelson et al[18] and Merzenich.[40] As the frequency of stimulation dropped below 70-90 Hz, both C.R. and J.B. reported that the sensations began to "flutter."

C.R. could distinguish variations in stimulation frequency as small as ±25 Hz over the range of 25-400 Hz as changes in pitch. J.B. required changes of about 50-80% of the stimulation frequency before he was able to detect changes in pitch. Although it is tempting to attribute this difference to J.B.'s prelingual deafness, data must be obtained from many more patients before this explanation can be verified.

Initial pitch scaling experiments conducted with D.C. also demonstrate the place and periodicity pitch phenomenon.[63] These experiments were conducted by randomly presenting all possible combinations of the six intracochlear electrodes, stimulated at three different frequencies (100 Hz, 175 Hz, and 300 Hz) ten times each.[61] The subject was instructed to assign a number to each presentation based on the pitch of that presentation. Figure 20 shows representative results for stimulation frequencies of 100 Hz and 175 Hz. The trend for pitch to increase with increasing electrode number and increasing stimulation frequency is evident. Similar results have been obtained with J.S.

If single biphasic pulses were presented, all patients reported a "ping" sound with a distinct pitch. Initial experiments demonstrated that the pitch of this sound could be modified by changing the pulse width of the stimuli. For example, when J.B. listened to A/B comparisons of single pulse pairs with pulse widths of 0.25 msec and 0.025 msec, he described the latter as higher in pitch.

Pitch Continuum. When C.R.'s most apical electrode (electrode 1) was activated at the same frequency as electrode 2 he stated that electrode 2 produced a higher pitch. Based on the periodicity pitch phenomenon, decreasing the stimulation frequency of electrode 2 should result in a decrease in pitch, while increasing the frequency of electrode 1 should cause an increase in pitch, and thereby reduce the difference in pitch between the two electrodes. In fact, when electrode 2 was activated at 75 Hz (just above "flutter") and electrode 1 was stimulated at 400 Hz, C.R. reported that the two were the same pitch.

Similar experiments were conducted with D.C. to determine how the place and periodicity phenomena combine to determine pitch. The method, results, and implications have already been described,[61] but representative results are presented in Figure 21 to demonstrate the pitch continuum possible when place and periodicity effects interact.

In similar experiments with J.B., periodicity pitch was used to reduce the

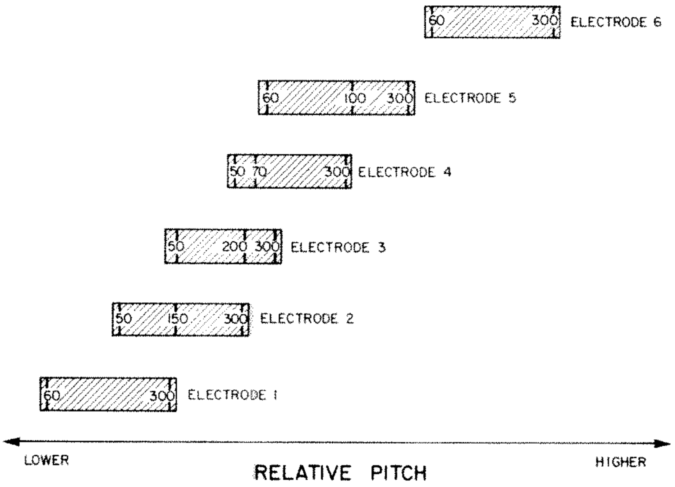


Fig. 21. (D.C.) Summary of the combined effect of place and periodicity pitch derived from A/B comparison experiments. The numbers within the rectangles indicate representative stimulation frequencies at particular electrodes. The position of a stimulation frequency within its electrode rectangle indicates its pitch relative to other stimulation frequencies at the same and different electrodes.

difference in pitch produced by two electrodes. These differences have never been reduced to zero, as with C.R. and D.C.

Tune Recognition. A preliminary experiment in tune recognition using the periodicity pitch phenomenon was encouraging. As reported in more detail elsewhere,[61] the first four bars of the five tunes used were slightly modified so they could be played with 16 quarter notes. This eliminated any rhythm cues. Each note was assigned a particular stimulation frequency and then the five tunes ("Frere Jacques," "Mary Had a Little Lamb," "Yankee Doodle," "Twinkle Twinkle Little Star," and "This Old Man") were played using electrode 3. D.C. spontaneously recognized "Mary Had a Little Lamb," "Yankee Doodle," and "Twinkle Twinkle Little Star." He did not spontaneously recognize any of the tunes at the other electrodes, presumably because the pitch intervals between notes for the given stimulation frequencies were not consistent with the musical scale at these electrodes.[61]

ABSOLUTE DATA OBTAINED FROM A UNILATERALLY DEAF VOLUNTEER

The data reported in this section were obtained from experiments conducted with P.H., the unilaterally deaf volunteer. Because only the two most apical electrodes of P.H.'s array seemed to overlay excitable tissue, the experiments described here include only these two electrodes. The stimuli were biphasic, pulsatile waveforms with pulse durations of 0.25 msec.

Pitch-matching Experiments in the Operating Room. Before P.H.'s electrode array was implanted, a single electrode calibrated from the tip every 5 mm was inserted through the round window approximately 25 mm into the scala tympani. Since the patient was under local anesthesia, we were able to conduct pitch-matching experiments using the Method of Adjustment at this and subsequent electrode positions as the electrode was pulled out. At 25 mm, the pitch elicited by stimulation at 200 Hz matched acoustic tones of 1500 Hz. After the electrode was pulled out approximately 6 mm (leaving it 19 mm within the cochlea), another match was made at an acoustic frequency of 2000 Hz. The electrode was then positioned approximately 6 mm within the cochlea and no response was elicited. These pitch-matching data are consistent with frequency versus distance relationships

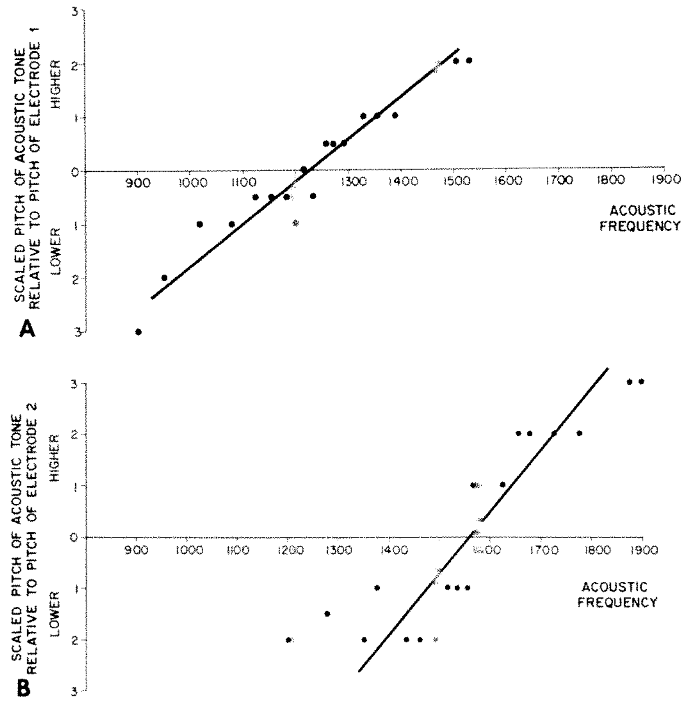


Fig. 22. A) (P.H.) Pitch of the acoustic tone heard in his normal ear, scaled relative to the sound elicited by activating electrode 1 and plotted as a function of the acoustic frequency. The stimulation parameters of electrode 1 were held constant at a frequency of 200 Hz (pulse duration: 0.25 msec). As expected, the scaled value of the acoustic pitch produced by cochlear stimulation as acoustic frequency increased. The crossover point at approximately 1225 Hz gives the approximate pitch of the sound elicited by cochlear stimulation and is consistent with the tonotopic map of the cochlea. B) The experiment illustrated here was conducted in the same manner as the one shown in (A), but in this case, electrode 2 was activated and the crossover point occurred at 1560 Hz. Comparison of the data illustrated here and in (A) clearly demonstrates place pitch.

derived from motion of the basilar membrane.[62]

Pitch-matching Experiments After Implantation. Initial pitch-matching experiments with P.H. after implantation were conducted by the Method of Adjustment. P.H. controlled the frequency and intensity of the tones and was instructed to match the tone heard in his normal ear with the sound elicited by electrical stimulation in his deaf ear. The acoustic and cochlear stimuli were presented alternately for durations of 1.5 sec with a delay of 0.5-1 sec between each presentation while P.H. attempted to match the two.

The sounds that P.H. heard were somewhat "fuzzy" – unlike the relatively pure tones he had heard in the operating room. As a result, although the "fuzzy" sounds had a definite pitch quality (perhaps like narrow band noise), P.H. was unable to match this pitch with pure tones.

Another method of determining pitch yielded better results. First, a cochlear stimulus lasting 1.5 sec was presented, followed by an acoustic stimulus lasting 0.5-1 sec. P.H. was then asked to scale the pitch of the acoustic sound on a scale of ±3, depending on how much lower or higher the pitch of this sound was than the one elicited by electrical stimulation. For example, an acoustic sound that was much lower than the pitch he heard in his deaf ear was scaled as −3, while an acoustic sound that was slightly higher in pitch than the one produced by electrical stimulation was assigned a value of +1. The frequency of the acoustic stimuli was varied randomly while the parameters of cochlear stimulation were held constant.

Data obtained with electrode 1 at a stimulation frequency of 200 Hz are shown in Figure 22A. This plot indicates a crossover point between 1200 and 1300 Hz. A similar plot of data obtained with electrode 2 (Fig. 22B) indicates a crossover point at about 1600 Hz. These data demonstrate place pitch and are roughly consistent with electrode position (20 mm and 16 mm for electrodes 1 and 2, respectively) and tonotopic maps of the cochlea derived from basilar membrane motion and hearing loss measurements.[62]

These initial experiments indicate that the tonotopic map of the cochlea can be used to predict the pitch of implanted electrodes on the basis of their position within the cochlea. More work must be done in this area, however, to determine the effects of stimulation frequency and other stimulation parameters on the absolute pitch perceived.

CHARACTER OF PERCEIVED SOUNDS

From descriptions the patients have given us, we know that the sounds they hear in the implanted ear are not pure tones. When the unilaterally deaf patient compared sinusoidal and square-wave acoustic stimuli to sounds elicited by cochlear stimulation, he indicated that the square-wave sound was the better match, although it was not the sound he heard.

To determine exactly what patients do hear, it will be necessary to compare complex acoustic stimuli having a variety of spectral characteristics with perceptions elicited in the deaf ear. This may involve selectively filtering white noise with banks of adjustable analog or programmed digital filters.

DEVELOPMENT OF PITCH DISCRIMINATION WITH TIME

It is interesting to note that both P.H. and J.B. were unable to demonstrate place and periodicity pitch clearly for several months after implantation surgery. House's initial place-pitch results with C.R. were also marginal.[15] When we reinvestigated C.R. five years later, he demonstrated place pitch and periodicity pitch.[24] We also noticed that several months elapsed after implantation surgery before pitch discrimination was apparent with J.B. and P.H. Learning, neuronal plasticity, growth of a mesothelial sleeve over the electrode,[63] and recovery from surgical trauma are several possible explanations for this phenomenon.

DISCUSSION

FEASIBILITY OF AUDITORY PROSTHESES

The results of our research are encouraging from the standpoint of developing an auditory prosthesis. The success of the percutaneous connector described in the patients section has given us the experimental flexibility needed to quantitatively evaluate perceptions elicited by multichannel cochlear stimulation. Since the electronics can now reside outside the body, we have been able to develop a computer-controlled stimulation system that serves as a prototype prosthesis and therefore allows the range of experiments required to determine the feasibility of the multichannel intracochlear device we propose.

Place pitch has been demonstrated in relative terms in four bilaterally deaf patients and in absolute terms in one unilaterally deaf volunteer. Pitch-matching experiments conducted with the unilaterally deaf volunteer demonstrate that multichannel electrodes elicit pitch perceptions which are consistent with their position and the cochlea's tonotopic organization. This capacity to excite small segments of the spatially distributed auditory nerve is crucial for the development of a device that would enable the deaf to understand speech.

Recognition of tunes demonstrates the ability of one subject to associate and interpret perceptions elicited by intracochlear electrical stimulation in terms of past auditory experience.

Loudness matching experiments conducted with our unilaterally deaf volunteer suggest that loudness is related to the parameters of stimulation by an analytic expression. In addition, the small difference limens for loudness should allow a loudness continuum.

Finally, since the low levels of current required for cochlear stimulation can pass across the electrode-perilymph interface via double-layer charging, the toxic byproducts of electrolysis are minimized and the outlook for safe, long-term stimulation is good. The long-term stability of amplitude thresholds, electrode impedance, and perceptual effects are also encouraging from the standpoint of long-term chronic stimulation.

FUTURE DIRECTIONS

Although our findings are preliminary, they suggest several areas that will require substantial amounts of additional work.

Screening of Volunteers. Because more volunteers will be needed to determine whether the data we have observed can be generalized to a larger population of deaf individuals, the problem of identifying deaf volunteers with surviving nerve fibers distributed throughout the speech area of the cochlea is crucial. Without such volunteers it will be impossible to conduct the necessary experiments on pitch perception and speech synthesis.

Even though the unilaterally deaf volunteer who participated in our experiments responded well to promontory stimulation, he lacked excitable tissue under all but two of his five electrodes. Thus the development of a minimally invasive, preoperative procedure for identifying the spatial distribution of surviving nerves is crucially important.

Additional Pitch-matching Experiments. More pitch-matching experiments must be conducted to determine not only the percise relationship between perceived pitch and stimulation parameters but the variability of this relationship in the deaf population of interest. Additional experiments will also be required to determine whether the expression for relating loudness and stimulation parameters can be extended to the deaf population as a whole.

Stimulation with Multiple Electrodes and Synthesis of Complex Sounds. Once the absolute perception of pitch is characterized in terms of electrode position and parameters of stimulation, it will be possible to investigate the synthesis of complex sounds by multichannel stimulation based on the spectral characteristics of these sounds. The ability to present complex sounds to the deaf by this method will be the next milestone in the development of a cochlear prosthesis.

Determining the Essential Characteristics of Speech. Establishing the characteristics of the acoustic waveform that produce intelligible speech is important for two reasons. First, it will aid us in encoding the acoustic waveform as electrical stimuli; second it will reduce the amount of information that must be transmitted for speech discrimination.

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EXPERIMENTAL OBSERVATIONS
of
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following
SEGMENTAL REMOVAL, FREEZING, & REIMPLANTATION

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EXPERIMENTAL OBSERVATIONS OF CANINE MANDIBULAR REGENERATION FOLLOWING SEGMENTAL REMOVAL, FREEZING, AND REIMPLANTATION

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SEATTLE, WASHINGTON

Mandibular replacement subsequent to major extirpative head and neck surgery is predisposed to complications in the best of hands. The most suitable prosthesis appears to be the previously resected mandible, both from the standpoint of antigenicity and configuration. This study establishes that in the canine mandible a healthy, revitalized osseous network is reestablished subsequent to resection, freezing and replacement of the mandibular body when the graft is immobilized. The neoosteogenesis is borne out by in vivo (technetium 99, methylene diphosphonate scanning) and histopathological (tetracycline fluorescence and polarizing microscopy) studies. This early work in the canine suggests the potential for application in the human when the procedure is further refined and perfected.

The management of malignant tumors of the floor of the mouth involving the mandible almost always elicits dissatisfaction on the part of the surgeon. There are multiple solutions to the problem. Every solution, however, carries with it a relatively high incidence of failure and temporary complication. The main focus of failure in reconstruction is the mandible. Although Marchetta et al[1] have shown that marginal resections can and should be used more frequently, the situation still arises where the anterior arch of the mandible must be resected to encompass the lesion and insure an adequate resection margin. The creation of a healthy, cosmetically appealing replacement for this bone is a major goal of the therapeutic procedure.

REVIEW OF LITERATURE

Various types of grafting material have been used.[2-5] Xenografts have not been helpful at all in providing a solution to the problem. Allografts (homografts) demonstrate a fairly high level of antigenicity and are frequently rejected and reabsorbed by this mechanism. Alloplastic grafts comprising synthetic materials such as ceramics, polyvinyl chloride, acrylics, Vitallium® mesh, Vitallium® or chrome plates, etc., have not been consistently successful due to rejection either intraorally or extraorally secondary to fistula formation.

Autografts have thus far provided the best solution to the problem.[6-9] The rib and the iliac crest are the most common choices for donor material. Of the autografts, particulate marrow and cancellous bone have been physiologically most active in osteoblastic activity. The ultimate autogenous material appears to be the patient's own mandible because of the total absence of immune rejection and obviation of the need for graft reshaping. Mandibular autografts have been used by several investigators[10-14] subsequent to devitalization either by extreme heat or extreme cold.

Some reasons for failure of freeze-dried homografts of bone applied to all of the methods used. Marble[11] cited failure from placement of bone chips in contaminated areas or failure to avoid oral contamination at the time of the procedure. The freeze-dried bone was thought to go through several stages as it was transformed into new bone. The initial stage of apparent inactivity was followed by new bone formation around

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the graft with subsequent slow graft resorption and replacement with new bone. The process was accelerated, however, by implantation of active autogenous bone marrow into the freeze-dried mandibular replacement.

The procedure of introducing cancellous bone chips containing a large amount of marrow into the wound site has enhanced the chance for survival of autogenous grafting material. The iliac crest is considered to be the best donor site by offering a large amount of bone and marrow with a relatively low morbidity and inconvenience to the patient. Size of the graft has some bearing on the success of the procedure. Mohnac[3] has documented that a smaller graft faces a better prognosis than a larger one because of a diminshed chance of long-term hypovascularity in the mid-portion of the graft.

Boyne,[2] Rappaport et al,[15] and Boyne and Sarum[16] have developed a procedure employing particulate marrow and cancellous bone chips resting on a Vitallium® metal tray which is used as a support and an internal split. This tray is attached to the remaining mandible using a minimum of two screws at both mandibular ends. A Millipore® filter is used to line the tray. This allows diffusion of extra cellular fluid requisite for new bone growth, but inhibits ingrowth of fibrous tissue. The osteogenic activity can ensue at a rapid rate if cancellous bone marrow is placed in an environment of decreased fibroblastic activity. These authors also believe that the permeable barrier graft can maintain bulk and contour in greater volume than the solid graft.. Radiotherapy is not considered to be a contraindication for immediate grafting; however, shaped iliac crest filled with particulate marrow and cancellous bone is used instead of the metal crib. Branemark et al[4] have used this latter technique and advocated replacing the mandible immediately to aid in molding and in developing local nutrient for bone. Postoperative interocclusal fixation was not found necessary.

Snyder et al[17] and Conley[18] have developed a procedure that is somewhat beyond the scope of this subject. This entails replacement of the mandible with a compound bone flap within a skin conduit. The clavicle is usually the donor bone, and is incorporated in a large deltopectoral flap. These regional composite flaps are used when there is a large amount of soft tissue replacement needed in addition to bone. Hopefully, the large vascular pedicle averts failure of bone replacement secondary to inadequate blood supply, inadequate coverage, poor approximation and infection.

In all of the preceding solutions to the problem, the bone has been brought in, borrowed, reshaped and implanted into the area of mandibular deficit. The best solution appears to be to use the patient's own mandible after any vestige of tumor has been devitalized or removed. Harding[10] reinserted the patient's mandibular segment subsequent to devitalization by boiling. In 15 patients he noted that the bone was gradually replaced by fibrous tissue and demonstrated no osteogenic potency, but all of these patients achieved adequate function. Harding emphasized that this should only be done when one can obtain good oral closure and good soft tissue sleeve cover over the reimplanted bone. Alvarado et al[9] have cited two failures of such treatment.

Some method must be devised to utilize the patient's mandibular arch and allow for reinstitution of osteoblastic activity. As discussed later, freezing in conjunction with particulate marrow and cancellous bone grafting may provide the ultimate solution.

Some basic concepts should be reviewed to clarify the problems and perhaps direct us toward a solution. Trueta[19] has shown that a rich blood supply is necessary for bone growth; periosteal and nutrient blood supply play a role in fracture healing. He has also shown that a periosteal hematoma may help with early neovascularization, which in turn leads to osteoblastic ingrowth. The endosteal callus is important as well; but this leads to ingrowth of fibroblasts, which subsequently inhibits development of a new blood supply and osteoblastic activity. Fractures healing by endosteal callus alone heal slowly. Suppression of the peripheral callus by plates and screws also delays healing. According to Thompson and Casson[20] periosteum plays a large osteogenic role, especially in onlay grafts. The endothelium of ingrowing capillaries may be an essential source of osteogenic cells. A cancellous surface of the onlay graft approximating the cancellous surface of the host bone results in the most favorable setting for survival of the graft. When the cancellous bone is placed outward and the periosteal surface inward, revascularization and osteocytic repopulation are enhanced, but the size of the onlay graft is diminished because of resorption.

Richter et al[21] demonstrated that when fibrous tissue is suppressed and prevented from entering the site of osteogenesis, the graft material within is more able to complete reossification. The osteogenic potential of hematopoietic marrow is well documented by Rappaport et al.[15] It is of interest that both the Millipore® filter and cortical bone act as barriers to fibrous tissue invasion and proliferation.

Obviously the major problem with homograft bone is rejection by the host. The major antigenic component of fresh bone grafting material is the marrow, although there is some demonstrable antigenicity to cortical bone according to Burwell et al.[22] Frozen bone shows diminished but persistent antigenicity, whereas boiled bone and freeze-dried bone elicit no antigenicity. It is accepted that autogenous bone is far superior to homologous bone as grafting material. Fresh bone is better than frozen bone which in turn is better than dried bone.

What has been the experience with freezing of bone? It has been shown by Emmings and Gage[23] that one can obtain bone devitalization by freezing for five minutes at a temperature below −40 C. Gage et al,[24] and Gage[25] detemined also that freezing long bones in vivo for as little as five minutes resulted in complete cellular destruction and that six months were required for replacement. The process of healing and replacement of the necrotic periosteum begins at the periphery. Subsequent to the periosteal regrowth new bone growth occurs peripherally as well. The medullary component is hindered by fibrous tissue ingrowth in response to necrotic marrow. They believe that cryosurgery is applicable as a primary treatment for some bone tumors. It can destroy all cells in a given segment of bone, but persistent tumor cells can result in failure.

Stone et al[26] have outlined the physiological mechanisms whereby the bone cells vary. The freezing injury causes cell death by increasing intracellular solute concentration and the formation of intracellular ice crystals. There is variability of response of different cells in terms of resistance to freezing effects. More rapid freezing caused smaller ice crystals, thereby causing more injury. In vitro studies have shown cancer cells to be more susceptible to double freezing techniques and that cell viability decreases from 0 to −40 C. Cancer cells appear more susceptible to freeze and thaw if done at the level of −20 C.

Smith and Weaver[27] have reported a series of 50 patients who have received cryosurgery as definitive therapy for intraoral tumors. In only 4 of 25 patients who had superficial bony invasion or tumor immediately adjacent to the periosteum was resection necessary for residual disease. This study documented the therapeutic potential of cryosurgery. Weaver and Smith,[13] in addition, reported the removal and subsequent implantation of mandible in six patients after freezing to a cellularly destructive level of hypothermia. Two of the six patients treated in this fashion failed, one because of residual tumor. The fate of the other two was not documented. This contribution suggested that the concept is valid and that there is potential benefit and reason for exploring this procedure further.

Marciani and Bowden[28] and Marciani et al[29] have recently reported their experiences with partial excision of the canine mandible, freezing, and reimplantation with internal fixation. In their experiments the frozen bone was

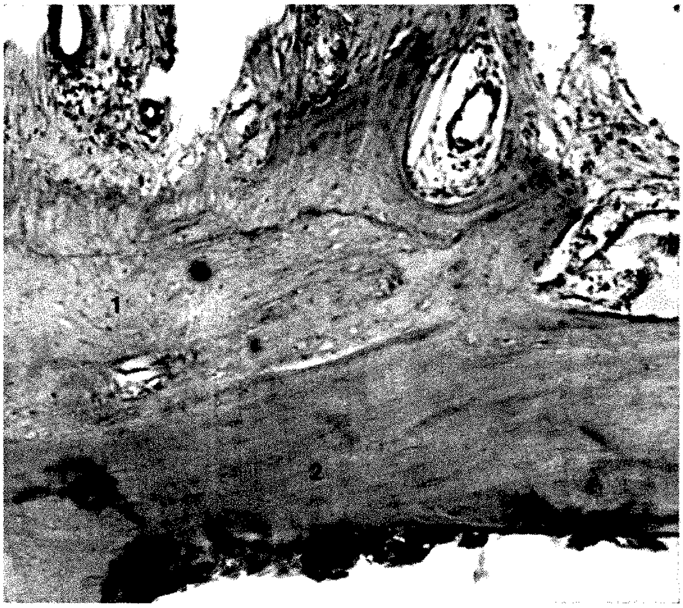

Fig. 1. Ten weeks following mandibular resection, freezing and replacement. No. 1 - Active new bone growth with dilated haversian systems; No. 2 - Devitalized lamellar bone.

treated as a template over which the periosteum formed new bone and the endosteum followed suit, but at a later date. The character of the mandibular bone changed from woven to lamellar as the grafts grew older and more mature. They noticed also that the dimensions of all grafts were smaller than they were previously and that callus information was always more pronounced on the lingual side of the osteotomy, thought to be due to a greater blood supply.

Despite this recent work on bone freezing and reimplantation, we still do not know what happens on a cellular basis, nor are we certain what the method of reossification is, nor how we can enhance it. There is no doubt that if freezing and reimplantation can be perfected as a procedure, much will have been accomplished toward our goal to eliminate some of the cosmetic side effects of curative extirpative surgery for intraoral carcinomas. It seems most desirable to establish the pattern of bone growth and reossification subsequent to freeze and thaw techniques. What Weaver and Smith[13] have shown clinically in the in vivo situation should be documented experimentally prior to any aggressive clinical application. Segmental resection, freezing, and replacement of the mandibular segment warrants a histopathological survey.

METHODS AND MATERIALS

Stage 1. In each of six dogs, a segment of the inferior aspect of the body of the mandible (4 x 2 cm) was resected bilaterally. On the right side, the periosteum was removed from the segment as well as from a 1 cm margin on either side. The periosteum was preserved on the left side.

In a control animal, the mandibular segment was removed, placed in saline for a ten-minute period and then replaced in the resection bed. In the remaining five animals, the mandibular segments were frozen twice for five minutes by immersion in liquid nitrogen. The thaw cycle was aided by immersion in 39 C saline. These segments were reintroduced into the mandibular bed and held in place with two No. 28 wire sutures. The wounds were closed undrained, and 1.2 million units of all-purpose Bicillin® were used for prophylactic coverage postoperatively.

Monitoring of bone replacement and neo-osteogenesis was performed by routing radiography, technetium 99m-methylene diphosphonate (Tc-99m MDP) screening as well as tetracycline fluorescence, and polarizing microscopy. Two animals were killed at each of three intervals (6, 10, and 16 weeks) following the initial surgery.

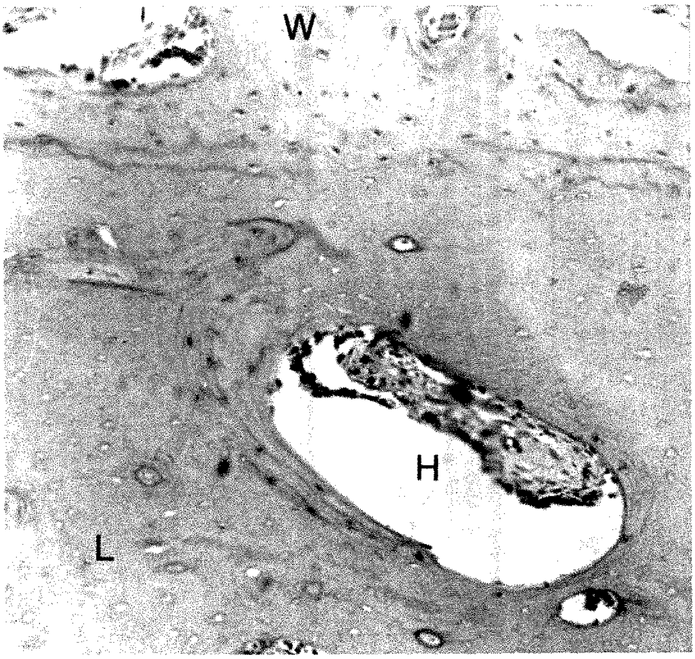

Fig. 2. Large haversian system (H) with extension of new bone formation into the devitalized lamellar bone (L) of a 16-week segment. New woven bone (W) is at the superior margin of photograph.

Milch et al[30] and Sissons and Lee[31] have utilized tetracycline and alazarin as markers to measure the rate of bone growth and metabolic activity. Both of these bone markers are accurate until the tagged bone is reabsorbed. In the process of using these agents it has been discovered that younger bone is more active than old, and that growth is more active near a blood supply. The two animals killed at the 16-week interval received tetracycline 1 gm a day for a three-day period, ten days prior to harvesting the mandibular segments. In both tetracycline-treated animals, the harvested bones were split longitudinally; one half was processed by routine decalcification procedures, and the other half, fixed in methyl methacrylate for sectioning and evaluation of fluorescence utilizing ultraviolet light techniques. The control mandible was harvested at the ten-week interval.

RESULTS

All of the mandibular segments showed active reabsorption of bone. Developing osteoid and neoosteogenesis were present as well. In the control animal, the segment showed evidence of cellular devitalization as evidenced by absence of nuclear material in the lacunae of the lamellar bone. Neoosteogenesis was present both in the lateral cortex of the mandibular segment and the medullary portion of the bone. This was apparent in the periosteum-deprived segments as well as the segments with intact periosteum. The most active area of bone replacement was the junction of the resected and host bone.

Frozen and nonfrozen segments could not be distinguished histopathologically.

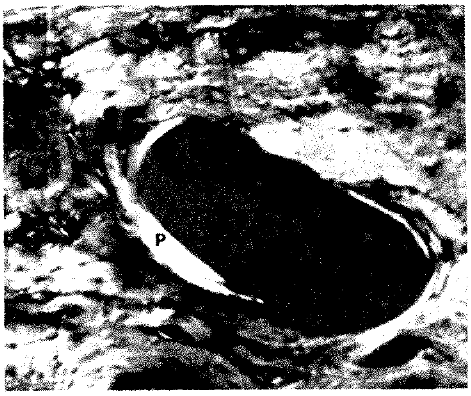

Fig. 3. A polarized view of the haversian system shown in Figure 2. The bright area (P) adjacent to the canal represents new collagen.

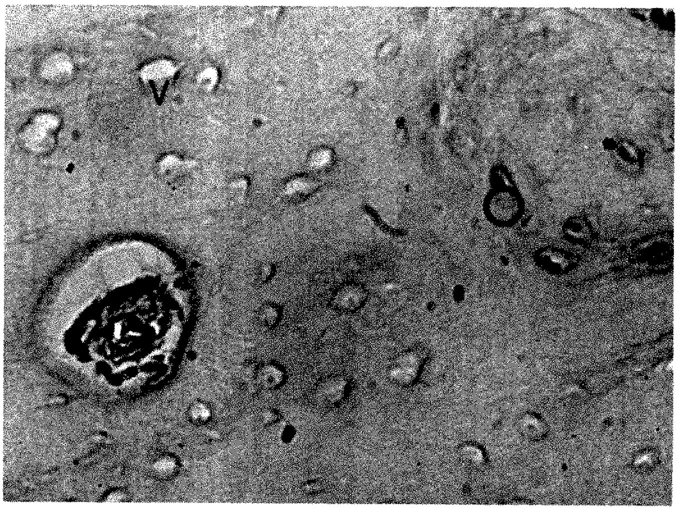

Fig. 4. A high power view of the extension of osteoblastic (O) activity into the devitalized lamellar bone and vacant lacunae (V).

Frozen segments at 6, 10, and 16-week intervals all showed evidence of partial replacement of the old bone with prolific formation of woven bone both externally and within the medullary space (Fig. 1). The 16-week bone segments demonstrated active neoosteogenesis with increased cortical thickness in the segments. In all mandibular segments, the haversian canals widened in the areas of bone reabsorption, again indicating an active remolding and revitalization process.

In addition to the normal reparative woven bone, there appeared to be utilization of the old devitalized lamellar bony matrix. In the 16-week segments, the haversian systems were filled with viable osteocytes and red blood cells (Figs. 2, 3 and 4). The lacunae adjacent to the haversian canals also contained viable cells. The peripheral lacunae, however, were still vacant. These findings were interpreted as extension of new bone growth by revitalization and subsequent replacement of the old lamellar bony matrix. Tetracycline fluorescence in addition to polarizing microscopy demonstrated new osteoid material in these haversian systems, confirming the viability of the mandibular segment (Fig. 5).

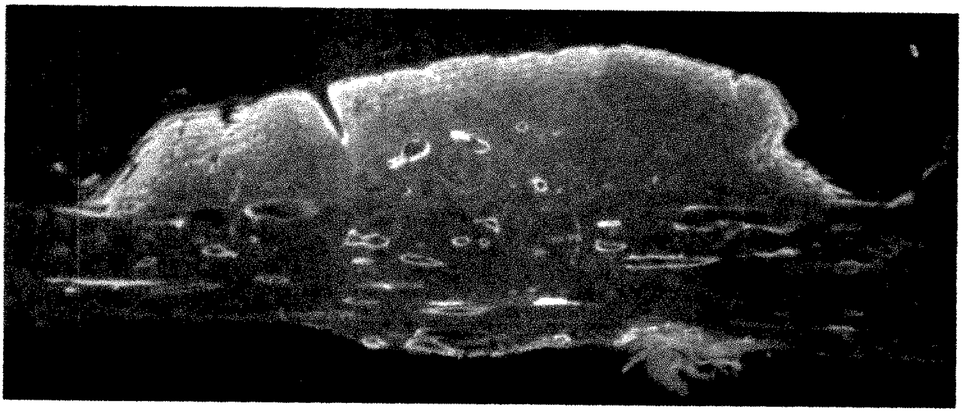

Fig. 5. A 16-week old specimen (No. 8958) showing exuberant appositional bone growth, highlighted by tetracycline fluorescence.

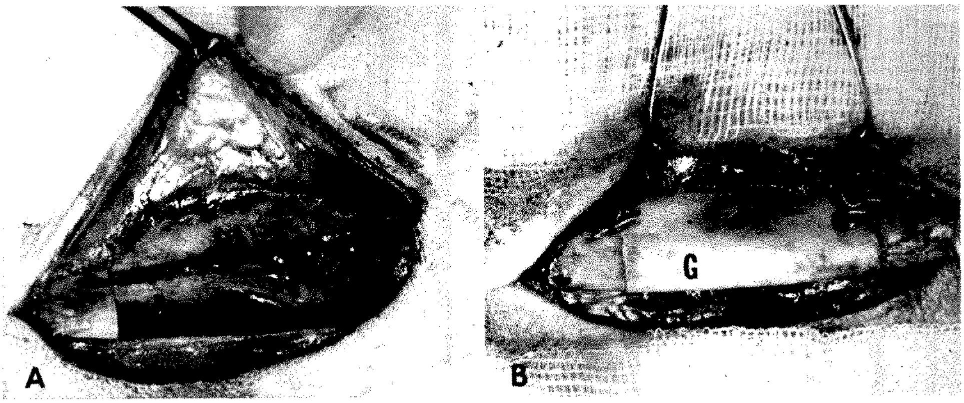

Fig. 6. A) An inframandibular incision has been used to gain access to the body of the mandible. A large segment of bone has been removed. B) The "treated" mandibular segment has been replaced and wired in place (G).

In all mandibular segments, the most pronounced osteolytic and osteoblastic activity was found near the margin of the resection in the area of highest local blood flow, confirming Truetta's findings. It was concluded that frozen bone, in the presence of a good blood supply became revitalized.

METHODS AND MATERIALS

Stage 2. Having established that reossification of a devitalized segment of mandible did indeed occur, it became necessary to simulate the clinical application more closely. This was best accomplished by using a larger portion of the mandible for resection with immediate reconstruction and long-term observation of the reparative process.

Four large dogs were made edentulous on the left side of the mandible. General anesthesia was used and care was taken to approximate the alveolar mucosa to prevent any focus of osteomyelitis. Three weeks later, a large portion of the body of the left mandible (at least 4 cm in length) was excised. Care was taken to avoid entry into the oral cavity along the alveolar ridge. This segment was then frozen at −186 C for five minutes, thawed in warm (39 C) saline immersion for ten minutes, and frozen again for five minutes (Fig. 6). After subsequent rethawing, the excised body of the mandible was replaced in its bed and fixed in place with two No. 28 wire sutures. An external biphasic fixation apparatus was utilized, consisting of Vitallium® screws affixed to the proximal and distal segments of mandible and held in position by a methyl methacrylate bar (Fig. 7). The replaced mandibular segment was completely immobilized in this fashion. Intraoperative and postoperative penicillin were used prophylactically. The dogs were placed on a soft diet

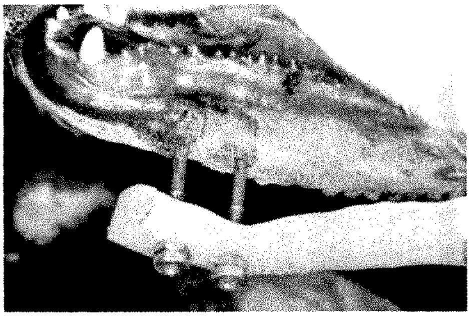

Fig. 7. An external fixation (biphasic) device has been applied for immobilization of the mandibular segment. The anterior portion (including insertion of Vitallium® screws into the mandible) is shown.

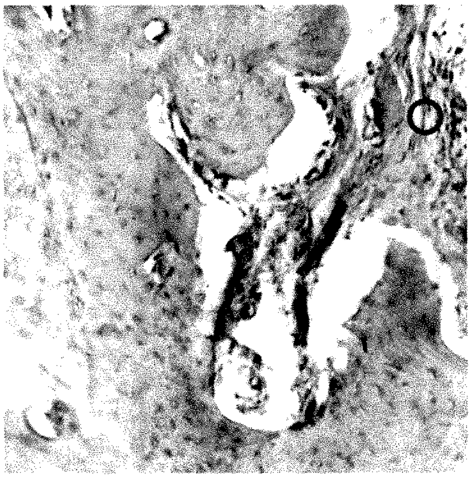

Fig. 8. A focus of osteomyelitis (O) is shown adjacent to healthy woven bone.

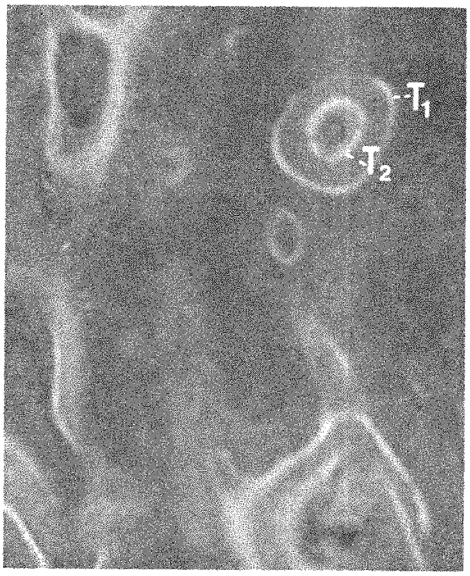

Fig. 9. High power view of segment of viable mandibular graft (No. 8272). The nonfluorescent area between the two areas of fluorescence outlines the dynamic process of new bone growth as shown by sequential (six-week interval) tetracycline administration (T_1 first tetracycline, T_2 final tetracycline).

for the duration of the experiment. The dogs were killed at four, five, 5½ and six months from the primary procedures.

Neoosteogenesis was evaluated in several ways. Tetracycline was given orally, 1 gm a day for three days, six weeks and again ten days prior to sacrifice in the five and six-month animals. One half of the mandibular specimen was processed in methyl methacrylate for fluorescent microscopy; the other half was decalcified, processed in the normal fashion and stained for histopathological interpretation.

Each of the four animals had monthly bone scans utilizing Tc 99m MDP. A comparison of the monthly scans allowed indirect observation of the neoosteogenesis. Routine radiological evaluation in one animal (No. 8272) was not found to be as helpful as mandibular scanning. Extensive loss of osteoid must be present before routine radiological techniques become helpful. Histopathological interpretation of H and E stains and polarizing microscopy were done on all specimens.

RESULTS

The four-month animal (No. 8868) demonstrated adequate healing as documented by bone scanning. However, there was medial deviation of the segmental graft. There were focal areas of osteomyelitis in the medullary portion of the graft, but there was complete union of the bone.

A five-month animal (No. 8272) demonstrated an area of persistently poor uptake on the Tc 99m MDP scan. On harvesting the mandible an area of bony sequestration was found and the focal areas of osteomyelitis in the medullary portion of bone were visualized histopathologically (Fig. 8). Tetracycline fluorescence revealed an active dynamic process of neoosteogenesis (Fig. 9).

Dog No. 9065 (5½-month animal), demonstrated an excellent uptake of the Tc 99m MDP agent, with some decreased vascularity at the proximal margin of the graft, indicating decreased vascularity and activity of new bone formation. Histopathologically, focal areas of osteomyelitis were seen as in the other segments, however, there was intact new bone bridging the grafted area.

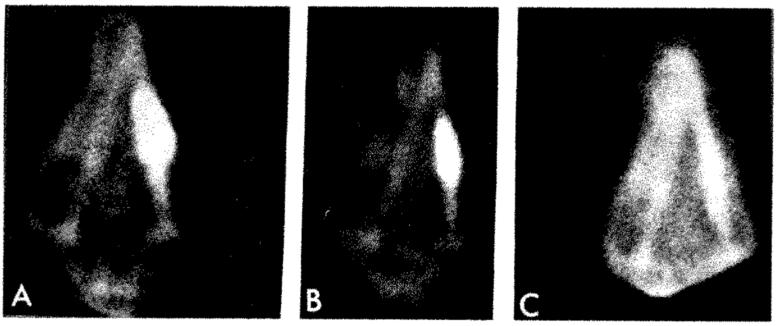

Fig. 10. Sequential Tc 99m MDP images (No. 8805) show active uptake of the bone seeker two months after grafting, with diminished uptake at the six-month stage indicating maturation of bone. A) 2 mos; B) 4 mos; C) 6 mos.

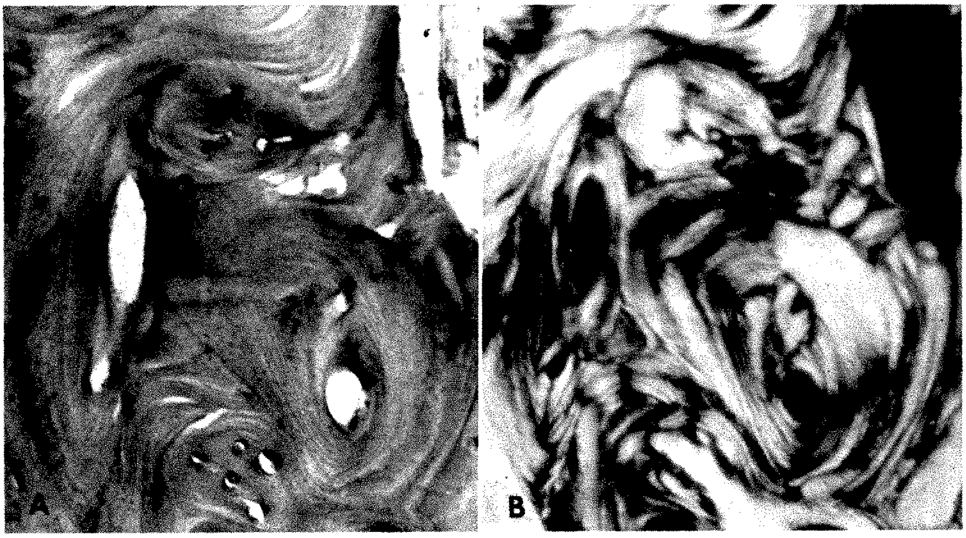

Fig. 11. A) High power view of a six-month specimen (No. 8805) showing woven-bone. B) A polarized view of A, highlighting the presence of woven collagen.

The final animal (No. 8805) was harvested six months after primary surgery. Tc 99m MDP bone scanning throughout demonstrated excellent vascularity suggesting good union. A relatively decreased uptake was apparent in the six-month scan, suggesting maturation of the bone graft and less active process of new bone formation (Figs. 10 and 11). Histopathologically, again, there was a well-healed union with a predominance of new woven bone in the graft area. Again there were focal areas of osteomyelitis in the medullary portion of the graft, adjacent to areas of healthy new bone.

DISCUSSION

Mandibular reconstruction in continuity with composite resection of a tumor of the floor of the mouth is still an unsolved problem. If the mandible is to be replaced by a prosthesis, it is most desirable that the prosthesis be adapted easily to the anatomical demands of the resection. Utilization of the patient's mandible is potentially a satisfactory solution, provided that the cellular structure can be completely devitalized by a tumoricidal process. The other requisite is that revitalization and reossification are allowed to occur. The injury caused by freezing appears to solve both of these requisites. Although there have been sporadic clinical reports of the use of cryosurgery in the management of intraoral tumors, there has not been any histopathological documentation of the effects of freezing on new bone growth.

This study has demonstrated that a segment of bone can be resected from the mandible, devitalized by freezing techniques, and revitalized after reimplantation into the host mandible. Revitalization and reossification is dependent upon an adequate blood supply, which accounts for the greater activity in the cortex of the segment as compared with the medullary portion of the bone segment.

At the 16-week interval, new bone growth is well established with woven bone being at least equal in thickness to the remaining lamellar bone. Those bones denuded of periosteum appear to do as well in regeneration as those that have the periosteum preserved. The greatest activity of bone growth in all of the segments is at the resection margins. This probably reflects the level of greatest vascularity and periosteal ingrowth from the periphery.

Longer term experiments involving large segments of mandible have shown that utilizing the host mandible is a justifiable alternative. Revitalization of large bony sections and a return to normal function have been demonstrated in this experiment. Despite the persistence of foci of osteomyelitis in the medullary portion of the bone graft, all of the mandibular segments developed bony union, only one of which (No. 8868), was marginal in terms of the amount of bone laid down.

The use of Tc 99m MPD as a bone seeker aids greatly in following the dynamic process of neoosteogenesis. It is especially valuable in the type of procedure employed here and should have application at the clinical level as well.

It is established that reossification takes place subsequent to cryogenic inury. It has also been established that utilization of the animal's own mandible as a homograft has a significant advantage over other materials.

Further questions have to be raised, however, regarding the philosophy of this procedure. The effects of preoperative and postoperative radiotherapy on neoosteogenesis and on the rate of secondary complications must be evaluated in the experimental animals. In addition, the role particulate marrow and cancellous bone might have in accelerating neooesteogenesis of the frozen bone must be evaluated. An increase in the rate of new bone growth would reduce the interval for potential development of complications. Answers to these questions are currently being sought.

CONCLUSIONS

1. Mandibular replacement subsequent to extirpative surgery is predisposed to complications.

2. The most suitable graft appears to be the previously resected mandible, both from the standpoint of antigenicity and configuration.

3. Exposure to devitalizing levels of ultracold eradicates any vestige of living cells.

4. Neoosteogenesis does occur in the devitalized bone provided there is ample vascularity and absence of overwhelming infection.

5. Long term follow-up subsequent to resection, freezing and replacement of the mandibular body usually demonstrates a healthy revitalized osseous network, provided the graft is immobilized. This neoosteogenesis is borne out by in vivo (Tc 99m MDP scanning) and histopathological (tetracycline fluorescence, polarizing microscopy) studies.

6. Further experimentation is being carried out to assess the potentially beneficial role of particulate bone marrow and cancellous bone as well as the potentially compromising effects of preoperative or postoperative radiotherapy.

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